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THIOURACIL IN THE TREATMENT OF THYROTOXICOSIS*

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A FEW cases of thyrotoxicosis must of necessity be treated by nonsurgical methods, and in some other cases such methods are preferable. Whether one can expect to treat most of the cases effectively by medical means is only conjectural, since the etiology of thyrotoxicosis and all the entities involved in its production are obscure. Thus far, the measures employed in the medical treatment of this condition, although quite effective in some cases, do not work out satisfactorily in the majority. Moreover, it is not known why iodine is effective in some cases and not in others, and its mechanism of action is uncertain. Such a state of ignorance induces one to approach the matter from various angles.

During the last few decades quite a large number of goitrigenous agents have been described. The effect of many of these substances has been attributed to the alterations in the iodine metabolism that they induce, since the simultaneous administration of iodine inhibits the goitrigenous effect. Certain other substances, such as cyanide, presumably induce goiters by inhibiting the biologic oxidation of the body cells. However, there have recently been described[1, 2] certain substances that induce goiter, presumably by their direct action on the thyroid gland. These are the sulfonamides, thiourea and thiourea derivatives. Following their administration to certain animals, particularly rats, thyroid enlargement results in a few days. Histologically, one finds hyperplasia of the acinar cells and a decrease in the colloid of the follicles. A drop in the basal metabolic rate occurs, and after a few weeks may be marked. These changes can be prevented by the administration of desiccated thyroid or thyroxin. They can also be prevented by hypophysectomy but not by the administration of iodine. In rats fed sulfaguanidine changes in the pituitary glands similar to those following thyroidectomy take place. These facts suggest that the above drugs act directly on the thyroid gland, inhibiting the production of thyroxin, this in turn leading to a decrease in the body metabolism and to an increased activity of the pituitary gland.

Astwood[3] tested the goitrigenous effect of a large number of sulfonamides and derivatives of thiourea. He found 2-thiouracil to be the most active substance tested. He used this substance in the treatment of 3 patients with thyrotoxicosis and found that it lowered the basal metabolic rate and caused a remission of symptoms, but when used for only a month a relapse followed its discontinuance. One of his patients, while receiving 2 gm. of thiouracil daily, developed agranulocytosis. Several patients with nonthyroid conditions treated with thiouracil experienced no drop in the basal metabolic rate.

During the last few months we have been studying some of the pharmacologic and therapeutic effects of thiouracil.§ In this paper we are considering its effect in the treatment of patients with thyrotoxicosis. We have treated all the patients with this disease whom we could find. All patients treated are included in this report. The case reports are given below, comment on them being confined chiefly to the factors that relate closely to the thyroid gland. In addition to the treatment with thiouracil we have given much attention to the patient's general condition. In most cases we prescribed supplemental amounts of thiamine, niacin, cevitamic acid and yeast. Several patients with menopausal symptoms were treated with diethylstilbestrol. All the patients were given sedatives at night. None of them were confined to bed. None of the patients were given iodine, with the exception of one who had syphilitic laryngitis, and in this case the iodine treat-

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§The thiouracil was supplied by the Lederle Laboratories, Incorporated, Pearl River, New York.

ment was not begun until after the basal metabolic rate had reached a minus level. All the thiouracil was given by mouth, usually in doses of 0.2 gm.

Case Reports

Case 1. V. S. (No. 1950T), a 27-year-old man, was admitted to the hospital on January 14, 1943, chiefly because of acute pharyngitis and laryngitis, which were treated with sulfadiazine. During the previous 6 months he had lost 40 pounds in weight, had become restless and nervous, and complained of intolerance of hot weather. Diarrhea was not infrequently present. He had also been bothered with palpitation and exertional dyspnea.

On physical examination the patient was apprehensive, restless and excitable. The skin was hot, moist, fine and smooth. No eye signs were present. The thyroid gland was enlarged diffusely to three times its normal size; it was firm and smooth, and a bruit was heard. There was a fine tremor of the fingers, tongue and eyelids. The pulse rate was 115 and the blood pressure was 140/70. The heart sounds were loud. A slight gynecomastia was present bilaterally.

On February 18, the basal metabolic rate was +66 per cent and the weight was 143 pounds. The protein-bound iodine of the plasma was greatly elevated (28 microgm. per 100 cc. — normal, 4 to 8 microgm). Treatment with thiouracil was started, the dosage being 0.2 gm. three times daily. After 2 days this was increased to 0.2 gm. five times daily. Within a few days there was a distinct clinical improvement and the metabolic rate began to fall (Fig. 1). On March 2, the dosage of thiouracil was increased to 0.2 gm. every 4 hours. By March 23, or 5 weeks from the initiation of the thiouracil treatment, the metabolic rate had returned to normal (+3 per cent). The dosage of thiouracil was gradually reduced to 0.2 gm. once daily. This dosage has been satisfactory in maintaining the metabolic rate at a normal level.

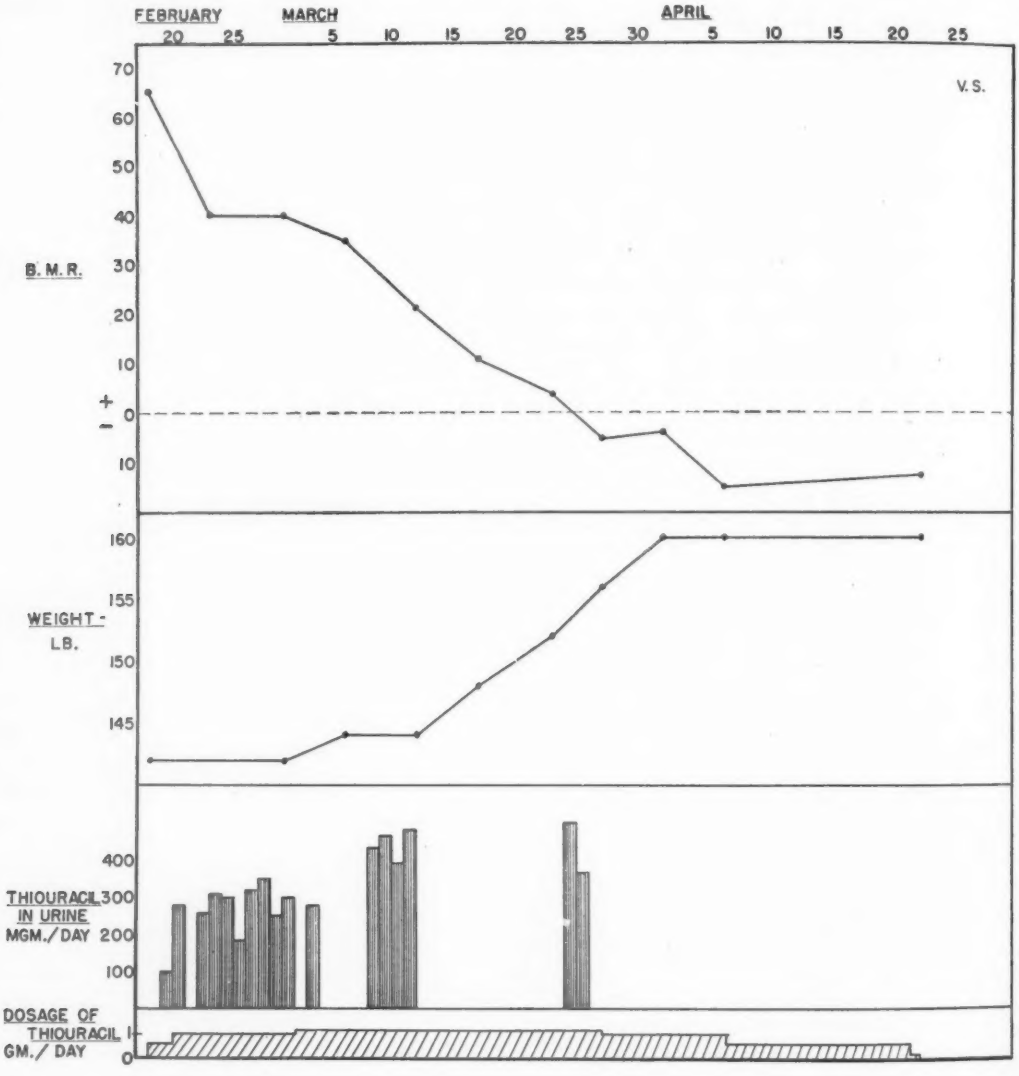
FEBRUARY
MARCH
APRIL
20 25 5 10 15 20 25 30 5 10 15 20 25
V. S.
B. M. R.
70 60 50 40 30 20 10 + 0 − 10
WEIGHT - LB.
160 155 150 145
THIOURACIL IN URINE MGM./DAY
400 300 200 100
DOSAGE OF THIOURACIL GM./DAY
1 0

Figure 1. *Case 1.*
Note the rate of excretion of the drug in the urine.

Associated with the drop in the metabolic rate there was a clinical response of equal degree. All the symptoms of thyrotoxicity disappeared. A definite effect was noticeable a few days after the treatment was started, but the most rapid response was from the 3rd to the 5th week. The patient gained 15 pounds in weight within 3 weeks. On May 15, the protein-bound iodine of the plasma was 5.1 microgm. per 100 cc.

During the first few days of treatment there was an increase in the consistence and size of the thyroid gland. Thereafter it became softer than at any time previously and decreased in size, although it was still above normal size. No eye signs of Graves's disease developed.

While the patient was receiving 1 gm. of thiouracil daily he excreted about 300 mg. in the urine per day. When the dosage was 1.2 gm., he excreted about 400 mg. per day. Stool specimens saved for a period of 4 days contained no thiouracil.

The patient was kept in the hospital for 6 weeks. Three weeks after discharge he was permitted to resume his work.

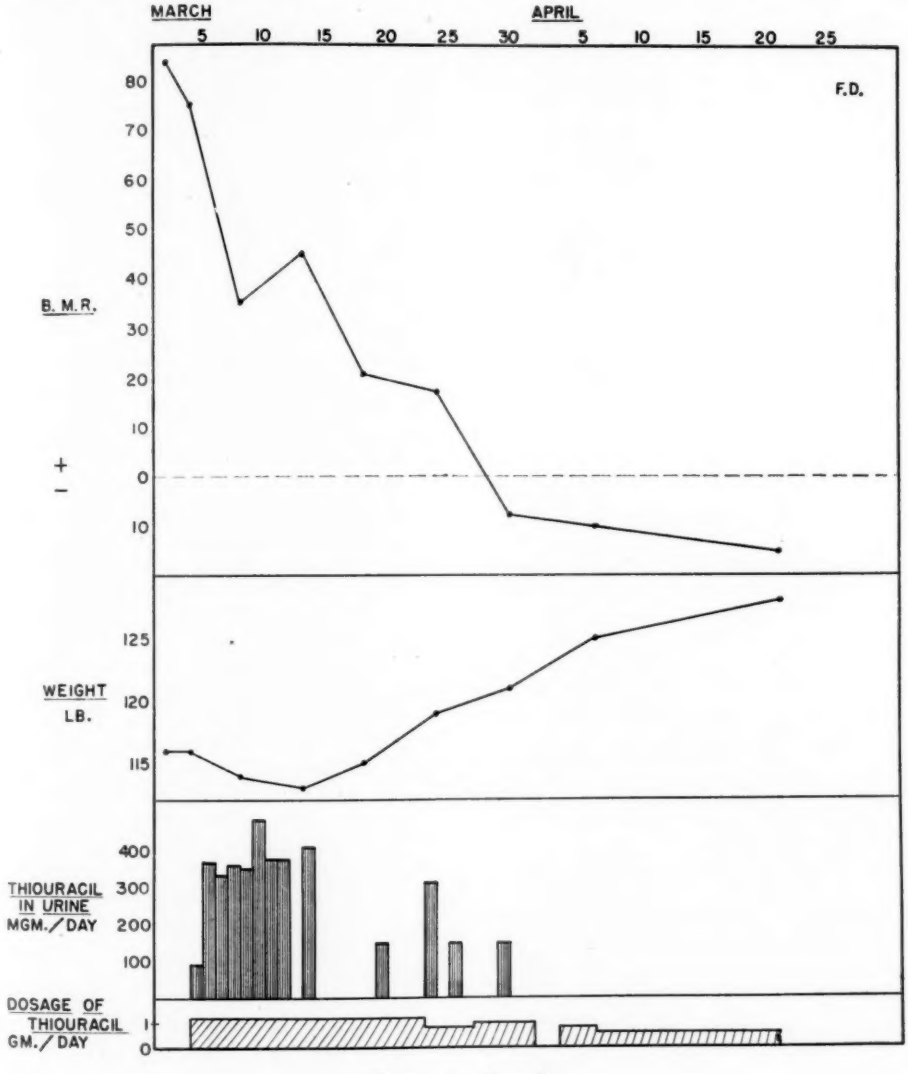

FIGURE 2. *Case 2.*
Note the amount of the drug excreted in the urine.

CASE 2. F. D. (No. 1098272), a 55-year-old painter, was admitted on February 27, 1943. The onset of thyrotoxic symptoms occurred 2 years before seeking treatment. The patient lost 24 pounds in weight, became nervous, perspired excessively and was troubled with palpitation and dyspnea. Only slight prominence of the eyes had been noticed.

On physical examination the patient was restless and excitable. The skin was hot, fine and sweaty. A marked tremor of the hands was present. There was slight exophthalmos — each eye measuring 18 mm. — with widening of the palpebral fissures, conjunctival injection, palpebral edema, slight chemosis and lacrimation. The thyroid gland was about three times normal size, firm and slightly nodular. There was slight cardiac enlargement. The pulse was grossly irregular in force and rhythm, having an apical rate of 170 and a radial rate of 110. The blood pressure was 130/70.

On March 2, the basal metabolic rate was +84 per cent, and 2 days later it was +74. On March 4, the patient began receiving 0.2 gm. of thiouracil every 4 hours.

He excreted about 350 mg. of this drug per day in the urine. The metabolic rate fell rapidly, reaching a normal rate (–7 per cent) in less than 4 weeks from the beginning of treatment (Fig. 2). On April 7, the protein-bound iodine of the plasma was 1.8 microgm. per 100 cc., which is definitely in the myxedematous range.

Concomitant with the changes in the metabolic rate there occurred a marked clinical improvement. All the symptoms of toxicity disappeared and the patient gained 12 pounds in weight. The auricular fibrillation ceased spontaneously early in the course of treatment. It reappeared but was stopped with quinidine and did not return. The thyroid gland became distinctly softer and somewhat smaller.

The condition of the patient's eyes was followed carefully because it was realized on the first examination that the changes in the eyes, although mild at the time, were of the type that leads to the classic state of so-called "malignant exophthalmos."[4] After having received thiouracil for 2 weeks, the ocular disturbances became more marked. There was a slight increase in the exophthalmos (measurement, 20 mm.), the lacrimation, the palpebral edema and the chemosis of the conjunctiva. Previous experiences with a large number of patients with this ocular complication[4] led us to conclude that desiccated thyroid is of advantage in the treatment of this condition. On April 9, after the basal metabolic rate had been maintained in a normal range for 10 days, the patient was given desiccated thyroid, 0.5 gr. per day. At the same time treatment for syphilis of the larynx was started. This consisted of weekly injections of 0.13 gm. of bismuth salicylate and 5 drops of a saturated solution of potassium iodide three times daily. The laryngitis improved rapidly, and there was no thyrotoxicity induced by the iodide, as occurred when Webster and Chesney[5] gave this substance to rabbits with goiters induced by cabbage. The eyes showed definite improvement, but this was more pronounced when the dosage of thyroid was increased to 1 gr. per day on April 21.

On April 12, 2 days after discharge, there developed swelling and slight tenderness of the submaxillary salivary glands. However, these glands subsided in spite of continued treatment with thiouracil.

The metabolic rate has been normal for the last 6 weeks, and during this time there has been no clinical evidence of thyrotoxicity. The patient has continued taking thiouracil daily, but the dosage has gradually been reduced from 1.2 to 0.4 gm. He is now working regularly as a painter.

Case 3. K. T. (No. 1099647), a 54-year-old woman, was admitted on March 11, 1943. Onset of thyrotoxic symptoms occurred 1 year before seeking treatment. The first manifestation was nervousness, leading to restlessness, insomnia, frequent crying spells and tremor of the hands. A short time later she began to lose weight, in spite of an increased appetite, having lost 22 pounds within a few weeks. She had no diarrhea. Her eyes developed a stare. She became sensitive to hot weather and perspired excessively. For 6 months she had experienced exertional dyspnea and swelling of the legs, the latter being more marked at night. For 3 months she had been treated by a physician for a toxic goiter, the treatment consisting of rest and large doses of sedatives, but no iodine.

On physical examination the patient was restless and emotionally unstable. The skin was hot, fine, moist and red. There was a marked tremor of the hands, eyelids and tongue. The eyes had a distinct stare but there was no exophthalmos. The thyroid gland was diffusely enlarged, being about three times normal size. It was firm and smooth in outline, and a distinct bruit was heard. The pulse rate was 105. The blood pressure was 140/75. The heart sounds were rapid and forceful.

On March 12, the basal metabolic rate was +80 per cent and the weight was 126 pounds. The protein-bound iodine of the plasma was 21 microgm. per 100 cc. Immediately thereafter the patient began receiving 0.2 gm. of thiouracil every 4 hours. With this dosage she excreted 400 mg. of the drug per day in the urine (Fig. 3). However, stool specimens collected for 4 days contained no thiouracil.

Within 3½ weeks after treatment with the drug was begun, the basal metabolic rate reached a normal range and has remained there during the subsequent 6 weeks that she has been followed. On April 12, the protein-bound iodine of the plasma fell to 5.7 microgm. per 100 cc. The clinical response has been in accord with the changes in the metabolic rate. The patient has gained 13 pounds in weight and all signs of thyrotoxicity have disappeared. The stare is no longer present and no other eye signs have developed. The thyroid gland increased slightly in size during the first few days of treatment. It then began to get smaller and softer, now being about twice normal size. A bruit is still present.

After having taken thiouracil for 3 weeks, in doses of 1.0 to 1.2 gm., the patient developed puffiness of the eyelids and definite edema of the legs. She had had edema of greater degree periodically during the preceding 6 months. On investigating the etiology of the edema no evidence of heart failure was found. The urine was negative; a phenolsulfonephthalein test was normal. The total serum protein was 7.38 gm. per 100 cc. and the nonprotein nitrogen 25 mg. However, the serum chloride was found to be 116 milliequiv. per liter. At the time that the edema appeared the basal metabolic rate was +1 per cent and the dosage of thiouracil was 0.2 gm. five times daily. This was reduced to 0.2 gm. three times daily, and within 3 days the edema disappeared and the serum chloride returned to normal, the metabolic rate remaining normal.

The patient was kept in the hospital for 1 month, had restricted activities for the next 2 weeks, and since then has carried out her usual program as a housewife. She is now taking 0.2 gm. of thiouracil per day.

Case 4. R. L. (No. 1099980), a 49-year-old factory worker, was admitted on March 15, 1943. She had not been well since the first onset of thyrotoxic symptoms 22 years previously. At that time she had three operations for toxic goiter, and following the last operation was told by her surgeon that she should never be operated on again. She experienced a distinct improvement following these operations but never became free of toxic symptoms. The patient, as well as her relatives and friends, had noticed that she always tended to be overactive and restless. The eyes remained prominent and she had had a goiter throughout most of the 22 years. There was a progressive loss of weight and strength until the patient became emaciated. During the year before admission the symptoms of toxicity increased, with further enlargement of the goiter, more pronounced sweating, nervousness, palpitation and weakness. During the few months before hospitalization there was a hacking cough, dyspnea,

orthopnea and transient edema of the legs. She had taken digitalis intermittently during this time. Throughout the 22 years she had periodically taken Lugol's solution, with some improvement in symptoms.

Physical examination revealed a tall, weak, emaciated woman, who was restless, apprehensive and irritable. The skin was hot, moist, smooth, fine and somewhat loose. Over the elbows and heels it was fiery red, owing to restlessness in bed. The eyes truly had the appearance of pop eyes, there being a pronounced stare and wide palpebral fissures. The exophthalmos appeared marked, but measurement showed it to be slight (20 mm.). No palpebral edema was present. The tongue was bright red. The neck was long and slender. A goiter was readily visible above the old thyroidectomy scar. There was two to three times the normal amount of thyroid tissue. It was hard and slightly irregular in outline, and a bruit was heard. The pulse was grossly irregular in force and rhythm; its rate was 110. The blood pressure was 120/60. The heart was moderately enlarged and its contractions were forceful. No murmurs were heard. There was slight pitting edema of the legs, and a few varicose veins. A fine tremor of the fingers was present.

The patient had a great fear of having another thyroidectomy and for this reason was constantly begging to leave the hospital. She refused to consider medical treatment of her toxic goiter because the many years of such treatment had fully convinced her that the condition could not be improved. She detested hearing the name "goiter" or anything pertaining thereto, because, as her sister stated, "it is like scraping an old and painful sore." The patient presented a good picture of a long-term thyrotoxicosis. Although weak and exhausted to the point of having to be supported in walking, she was begging to go back to work.

On March 16, the basal metabolic rate was +56 per cent. A few days later the patient began receiving 0.2 gm. of thiouracil four times daily. After 2 days, since she had not been upset by this medication, the dosage was increased to 0.2 gm. every 4 hours. On this dosage she excreted 250 mg. of the drug per day in her urine (Fig. 4). During the first 2 weeks of treatment she showed only slight improvement. The course was complicated by the development of several corneal ulcers in each eye owing to exposure during sleep. The diet was supplemented with niacin, thiamine, riboflavine, cevitamic

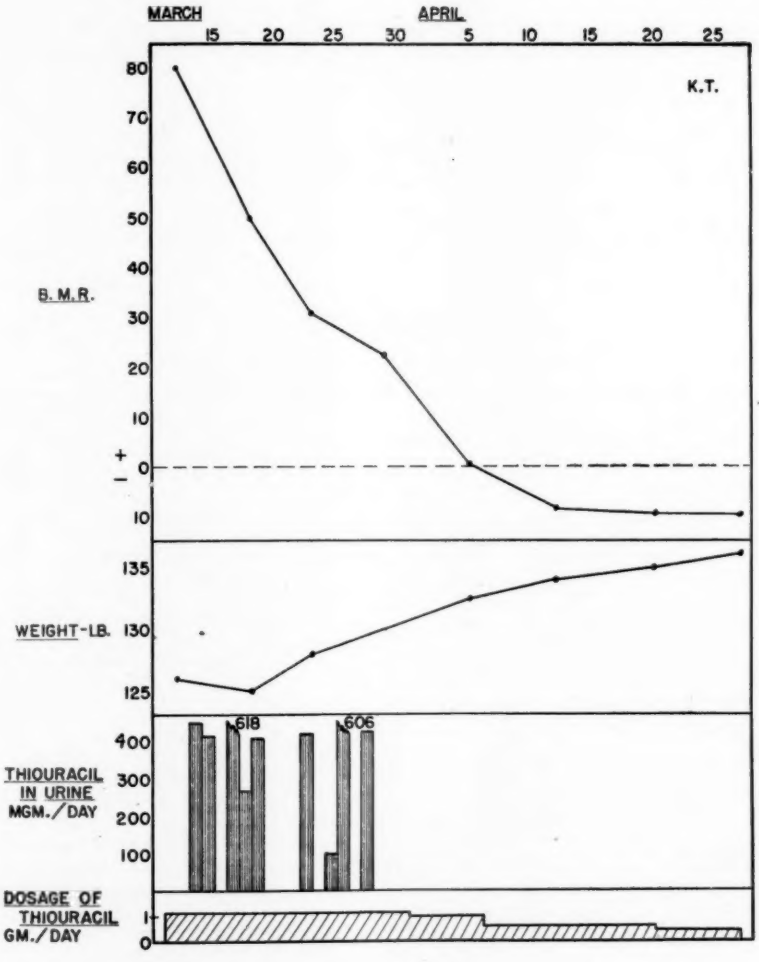

FIGURE 3. *Case 3.*
Note the rate of excretion of the drug in the urine.

acid and vitamin A. However, the condition of the eyes and the slowness in gaining weight caused her to be somewhat discouraged. In an attempt to break a vicious cycle she was given 10 mg. of methyl testosterone three times daily for 5 days (we hesitated to use larger quantities of this drug since it sometimes causes elevation in the basal metabolic rate).[6] The methyl testosterone appeared to have improved the patient's strength and mental attitude to a slight extent.

After having received treatment with thiouracil for 3 weeks the patient left the hospital, against advice, but carried on her treatment faithfully at home. During the 4th week of this treatment she improved rapidly and continued to do so. By May 11 she had gained 16 pounds in weight and the thyrotoxic state had disappeared. The eyes showed a decrease in stare. The amount of thyroid tissue had not changed much, but the gland was not quite so firm as originally. A distinct improvement in the cardiac status had occurred, but the auricular fibrillation was still present.

The patient so disliked basal-metabolism tests that she would not permit many of them. However, the tests that were run showed essentially a straight-line drop from +58 to +7 per cent. The dosage of thiouracil, which for the most part had been 0.2 gm. five times daily, has now been reduced to 0.2 gm. three times daily. The patient has been permitted to return to work.

Case 5. M. R. (No. 1101316), a 35-year-old housewife, was admitted on March 12, 1943. She had been well until 1 year previously, when she became restless, irritable, excitable and easily upset. Thereafter she experienced insomnia, heat intolerance, diarrhea, a loss of 20 pounds in body weight, slight exophthalmos, fullness in the neck, palpitation and exertional dyspnea.

On physical examination the patient was restless, apprehensive and excitable. The skin was hot, moist and smooth and exhibited vitiligo on the dorsum of the hands. There was slight exophthalmos and a small amount of palpebral edema. The thyroid gland was two to three times normal size, slightly irregular in outline and firmer than normal. The pulse rate was 110 and the blood pressure 130/75. The heart sounds were forceful.

On March 13, the basal metabolic rate was +45 per cent. On that date the patient began receiving 0.2 gm. of thiouracil five times daily, but only a few hours later left the hospital owing to her anxiety over her six children and her undependable husband. However, she continued the prescribed treatment at home, returning to the hospital at weekly intervals. The metabolic rate progressive-

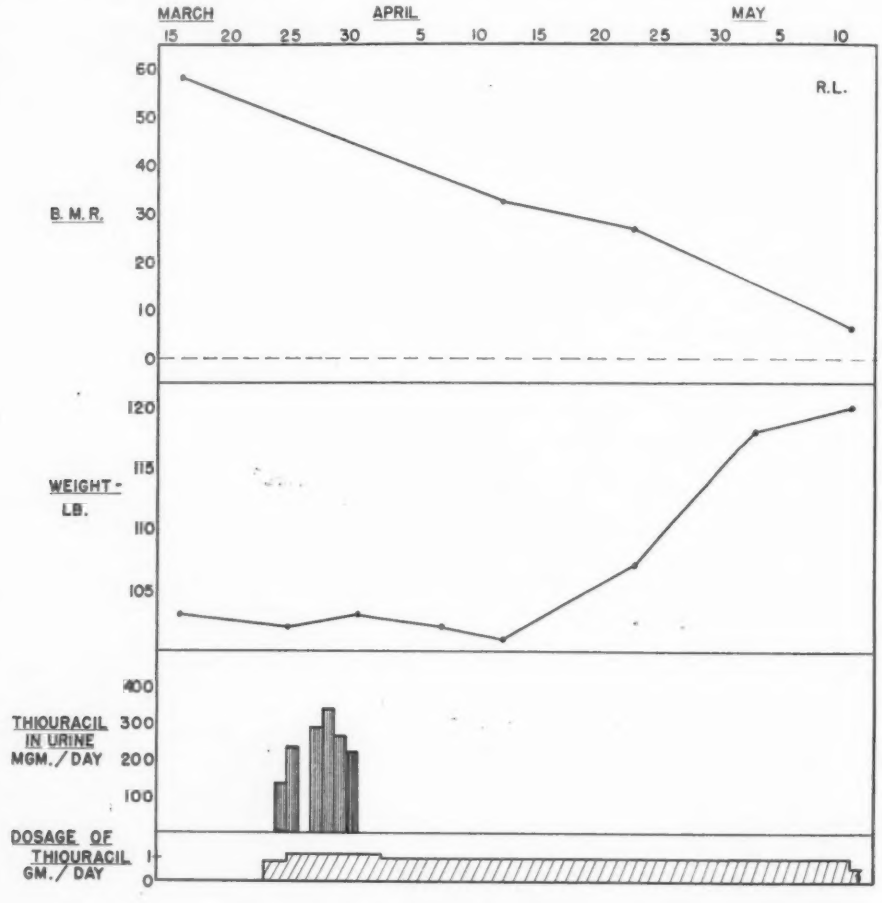

Figure 4. *Case 4.*

The infrequency of the metabolism tests was due to the patient's refusal to have them run.

ly declined reaching a normal level in 6 weeks (Fig. 5). It remained normal during the subsequent 3 weeks. Within the same time the protein-bound iodine of the plasma fell to a subnormal level (2.1 microgm. per 100 cc). Throughout most of the period of treatment the dosage of the thiouracil was 1 gm. daily, but it was gradually reduced to 0.4 gm. daily after the metabolic rate had become normal. The clinical improvement exceeded the response in the metabolic rate. Before the latter had become normal the signs of thyrotoxicity had disappeared and the thyroid gland had assumed an essentially normal size and consistence. There was a gain of 9 pounds in weight, but this occurred chiefly after the metabolic rate had become normal.

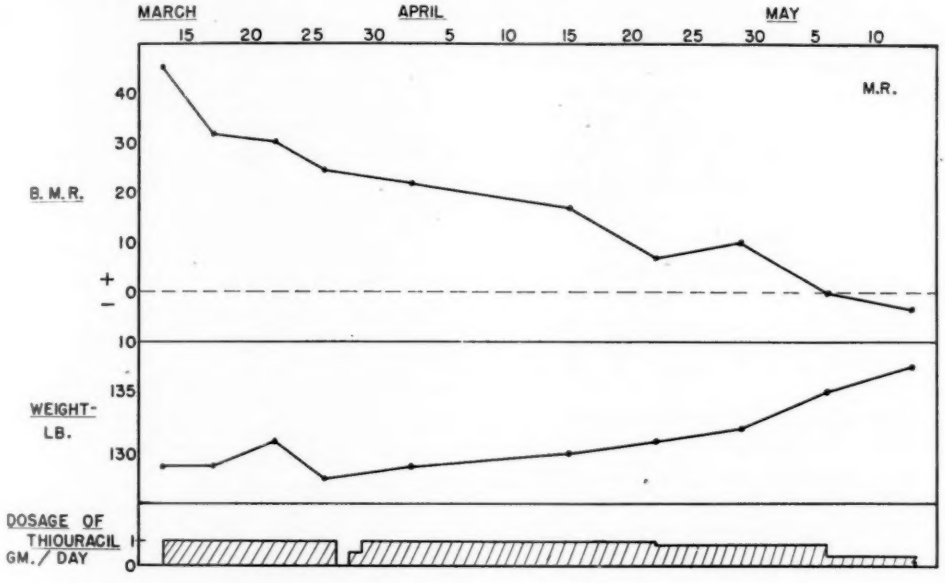

FIGURE 5. *Case 5.*

During the 2nd week of treatment the patient developed a very slight macular eruption. The phenobarbital that she had been taking was permanently discontinued and thiouracil was omitted for 1 day. The rash lasted only 2 days and did not recur in spite of the resumption of the usual dosage of thiouracil.

Throughout most of the course of treatment the patient has continued carrying on her household duties.

CASE 6. W. F. (No. 1103790), a 50-year-old Negro woman laborer, was admitted on April 19, 1943. Two years previously she had become nervous, with marked restlessness, excitability and emotional instability. In spite of a normal ingestion of food, she lost 44 pounds of body weight in 2 years. She usually had two bowel movements per day, although sometimes she had five or six. She noticed some puffiness of the eyelids but no exophthalmos. For 2 years she had had a fullness in the neck.

On physical examination the patient was restless, apprehensive and excitable. She cried several times during the examination. The skin was loose but otherwise not remarkable. There was palpebral edema and slight impairment to convergence, but no exophthalmos. The thyroid gland was enlarged to three times normal size, and was nodular and firm. The pulse rate was 96 and the blood pressure 170/80.

The basal metabolic rate on April 20 was +88 per cent. The following day treatment with thiouracil was started, the dosage being 0.2 gm. every 4 hours. Basal metabolic rates taken at weekly intervals were +55, +9, +18 and +5 per cent. In the meantime a marked clinical response occurred, essentially all the signs of toxicity disappeared and the patient gained 6 pounds in weight. She remained in the hospital for only 9 days and since then has carried on her work as a housecleaner. The thyroid gland has not shown much change in size but is a little softer. She is now taking 0.2 gm. of thiouracil three times daily.

CASE 7. R. F. (O. P. D. No. 434179), a 48-year-old housewife, was first seen on March 29, 1943. She had been somewhat nervous ever since her husband's death 6 years previously. However, she dated the onset of most of her thyrotoxic symptoms to a fire in her home 1 year previously, following which she became distinctly more restless, excitable and hyperkinetic and noticed a tremor, palpitation, exertional dyspnea, a goiter and a stare. She had been losing weight for 4 years, but during the past year had done so more rapidly, the total being 50 pounds in the 4 years.

On physical examination the patient was moderately restless and excitable. The skin was hot and slightly moist. There was a stare, lid lag and a slight impairment of convergence, but no exophthalmos or other eye signs. The thyroid gland was about three times normal size, firm and nodular and a bruit was audible. The pulse rate was 100 and the blood pressure 140/75. The basal metabolic rate was +53 per cent.

Hospitalization was advised, but the patient had so many duties at home that this could not be arranged. On March 31 she began taking 0.2 gm. of thiouracil five times daily. Metabolic rates determined at weekly intervals were +55, +38, +22, +19, +15 and +7 per cent. During this time the clinical response was in accord with the changes in the metabolic rate. All evidence of thyrotoxicity have disappeared. The patient

has gained 9 pounds in weight. The eye signs have disappeared. The thyroid gland has shown a distinct decrease in size and consistence but is not yet entirely normal. On May 12, when the basal metabolic rate was +7 per cent, the dosage of thiouracil was reduced to 0.2 gm. three times daily.

Throughout the course of treatment the patient has carried out her usual housework for a large family.

Case 8. R. J. (No. 1101981), a 49-year-old Negro woman, was admitted on April 2, 1943. Six years previously she had developed exertional dyspnea. This increased progressively and she found it necessary to sleep on two pillows. Subsequently she developed edema of the legs. Two years previously she became nervous, had three to four bowel movements per day, began to lose weight (a total of 40 pounds), developed swelling in the neck and became sensitive to heat. In July, 1941, she was hospitalized for a myocardial infarction. At that time the blood pressure was 160/90. There was mild congestive heart failure. While in the hospital the patient was found to have thyrotoxicosis with a basal metabolic rate of +31 per cent. She took potassium iodide, with a definite improvement in the clinical state and the metabolic rate. However, after a few weeks she discontinued the iodine and had an exacerbation in her symptoms.

On physical examination the patient was restless, excitable and apprehensive. The skin was moist, warm and fine. There was slight exophthalmos and palpebral edema. The thyroid gland was about three times normal size, firm and nodular. The pulse was rapid. The blood pressure was 190/100. There was slight cardiac enlargement but no congestive failure. The urine contained a small amount of albumin, a few white cells and an occasional red cell.

On April 3, the basal metabolic rate was +55 per cent. Two days later the patient began receiving 0.2 gm. of thiouracil every 4 hours. Examination of the urine showed that she excreted an average of 300 mg. of thiouracil daily during the period of 2 weeks' observation.

The basal metabolic rate at 10-day intervals was +55, +32, +22, +22 and +14 per cent. All symptoms of thyrotoxicity disappeared within 4 weeks. During that time the thyroid gland became definitely smaller and softer. The eye signs were never striking and did not show much change under treatment.

The patient was maintained on a daily dosage of 1 gm. of thiouracil for 5 weeks and the dosage was then reduced to 0.6 gm. daily, given in three doses.

Two weeks after she first began taking thiouracil she developed slight swelling of the legs. Urine examination gave the same findings as on admission and there was no evidence of heart failure. The serum protein was normal, but there were 118 milliequiv. of chloride per liter of serum. The carbon-dioxide combining power was 43 vol. per cent. In spite of continuation of the drug the edema disappeared within a few days and the chloride returned to normal, although the carbon-dioxide combining power remained slightly low (41 vol. per cent). However, the latter had also become normal within 2 weeks.

Case 9. L. S., a 31-year-old woman, was first seen on March 31, 1943. Three years previously she had developed the manifestations of severe thyrotoxicosis. A thyroidectomy was performed in August, 1941, and another in October, 1941, followed by a disappearance of the thyrotoxic state. However, 1 year later, during the 2nd month of her seventh pregnancy, the symptoms recurred. She became nervous and intolerant to heat. She noticed an increased prominence of the eyes, swelling of the eyelids, burning and itching in the eyes, tightness in the neck and palpitation. She lost 10 pounds in weight in 6 months, in spite of her pregnancy.

On physical examination the patient appeared only mildly toxic. The skin was slightly moist and hot. The eyes showed slight exophthalmos, with palpebral edema. There was about twice as much thyroid tissue as normal and the gland was of firm consistence. The fingers and tongue had a fine tremor. The pulse rate was 100. The basal metabolic rate was +36 per cent on March 31. On that date treatment was begun, using 0.2 gm. of thiouracil five times daily. She was not admitted to the hospital but came to the Out-Patient Department at weekly intervals. The metabolic rate fell to +27 per cent within a week, remained at that level for 3 weeks and then fell to +12 per cent, which is a normal level for a person 8½ months pregnant.

Clinically, the patient was free of all thyrotoxic symptoms within 3 or 4 weeks. The thyroid gland decreased to almost normal size and became softer. No definite change in the eyes resulted. She is now being maintained on 0.2 gm. of thiouracil three times daily.

Discussion

Absorption, Distribution, Excretion and Dosage

We have found, by the methods of Williams, Kay and Jandorf,[7] that thiouracil is rapidly absorbed and rapidly excreted. For example, to one normal person we gave 0.2 gm. of thiouracil and collected blood and urine samples at the following times: Fifteen minutes, thirty minutes, hourly through eight hours, two-hourly through twelve hours and twenty-four-hourly through three days. The highest blood level was found at fifteen minutes and was 2.3 mg. per 100 cc. Thereafter it fell rapidly until at eight hours only 0.3 mg. of the drug was present, but it did not entirely disappear from the blood until the third day. The most rapid rate of excretion of the drug in the urine occurred during the second hour, 15 mg. being excreted. Thereafter the rate decreased rapidly, only 12 mg. being excreted during the second twelve-hour period, and a total of 6.3 mg. during the second and third days combined.

When thiouracil is given in doses of 0.2 gm. at four-hour intervals, it requires about twenty-four hours to reach a more or less constant rate of excretion in the urine and a constant blood level. With such dosage the urine excretion is about 300 mg. per day, whereas the blood level is about 3 mg. per cent. When the above dosage has been maintained for several days, thiouracil can be found in the urine for six days or more after discontinuing the drug. When the dosage is 0.2 gm. three or four times daily, about forty-eight

hours is required to attain a more or less constant blood and urine level. Almost all the drug that is in the blood exists in the cells, the concentration in the white cells being many times that in the red cells. However, the latter contain a greater total amount of the drug.

It is obviously difficult to determine the distribution of the drug in the tissues of normal human beings. However, we have studied its distribution in the tissues of 2 patients dying from cerebral hemorrhage and 1 dying from bronchopneumonia. Totals of 1.0 to 3.6 gm. of the drug had been given to these patients. Most of the tissues, including that of the thyroid gland, had from 1 to 3 mg. per 100 gm. (fat-free dry weight). The concentrations in the adrenal glands, bone marrow and pituitary gland were greater than this. We have not been successful in finding thiouracil in any stool specimens.

Although the above studies represent a step forward in the estimation of the most desirable dosage and the intervals at which thiouracil should be administered, many more studies of this type are necessary. It would be particularly worth while to determine the optimum level of saturation of the thyroid gland and the dosage necessary to maintain this level. We are conducting such studies at present.

It is now our policy in the treatment of thyrotoxic patients, in the beginning, to give 0.2 gm. of thiouracil at four-hour intervals five or six times daily. With moderate clinical improvement and a drop in the metabolic rate, we reduce the frequency of medication to three or four times daily, spreading the interval as much as is convenient. After the metabolic rate is normal, we reduce the dosage to 0.2 gm. once or twice daily. Our present impression is that a dosage greater than this is not necessary and that a smaller amount will probably be satisfactory.

It will take some time to ascertain how long thiouracil should be given to a patient. On the basis of experiments with the use of iodine, although in many ways the two substances are incomparable, it seems advisable to give it for many months without discontinuation. Astwood et al.[3] found a recurrence of the disease in a patient although the latter had received thiouracil for about two months before it was discontinued.

Mechanism of Action

As indicated above, the data available at present suggest that thiouracil lowers the metabolic rate by inhibiting the formation of thyroxin. In the 4 cases in which we conducted iodine studies, we found that following treatment with thiouracil for a few weeks the protein-bound iodine* of plasma reached low normal or subnormal levels. Since the amount of thyroxin or thyroxin-like iodine of the blood is presumably an index to the amount of thyroxin produced in the thyroid gland, it seems clear that in some way thiouracil inhibits thyroxin production. However, the exact mechanism by which this is accomplished has not been elucidated.

On the basis of animal experiments,[1, 2] it was concluded that thiourea did not inhibit the stimulating effect of desiccated thyroid or thyroxin on the metabolic rate. We have investigated this phenomenon in human beings, using thiouracil. Two patients with myxedema were studied. In each case it was established, by methods which need not be mentioned here,[8] that the myxedema was primary in the thyroid gland. One patient, M. D. (Fig. 6), was found repeatedly to have a basal metabolic rate of about –44 per cent. She was given thiouracil, 1 gm. daily, for ten days, at the end of which time the metabolic rate was –47 per cent. With the continuation of the thiouracil and, in addition, the administration of 1.5 gr. of desiccated thyroid U.S.P. daily, the metabolic rate had risen to –17 per cent after twenty days of the combined treatment. Then with discontinuation of the thiouracil, but continuation of the thyroid, the metabolic rate became –25 per cent. The other patient, B. F. (Fig. 6), was found to have metabolic rates, before any treatment, of –26 and –36 per cent. After she had received thiouracil, 1 gm. daily, for nine days the metabolic rate was –25 per cent. With continuation of the thiouracil and the administration of 2 gr. of desiccated thyroid *U.S.P.* daily, the rate was –8 per cent. Thiouracil was discontinued for nine days while the thyroid treatment was continued, but no definite effect on the metabolic rate was observed. When thiouracil was again given for thirteen days, it had no effect on the rise of the metabolism induced by desiccated thyroid. Therefore, we may state that thiouracil does not lower the basal metabolic rate of untreated myxedematous patients, nor does it inhibit the response of the metabolic rate to desiccated thyroid.

We conducted an experiment with another patient, M. D. (Fig. 7), to ascertain whether thiouracil inhibits the goitrigenous and hypermetabolic effect of antuitrin T (thyrotropic hormone). The patient selected had been admitted to the hospital because of possible hyperthyroidism. On the basis of clinical grounds, we decided that she did not have a toxic goiter, but we have not completed the

*This is composed of the so-called "D" and "T" iodines, which are essentially equivalent, respectively, to the di-iodotyrosine and thyroxin contents of the plasma.

blood-iodine studies in her case. Particular attention was paid to the changes in the thyroid gland and the metabolic rate, in association with the administration of thiouracil, 1 gm. daily, for a period of twenty-two days. During the first ten days the patient was given daily 2 cc. (50 units) of antuitrin T in sesame oil. Within three days after this treatment was begun the thyroid gland had become definitely larger and firmer. Since the enlargement occurred so rapidly, we believe that it was due chiefly to the thyrotropic hormone injected. The metabolic rate not only failed to rise, but actually showed some decline (Fig. 7). Thus it appears that the thyroid gland had been stimulated to become hyperplastic but that its hypermetabolic effects were inhibited. Finally, the effect of thiouracil was tested in a patient, F. C. (Fig. 7), with a large colloid goiter. The drug was given for seventeen days, 1 gm. daily, but it was found to have no effect on the metabolic rate, or the goiter during this period of observation.

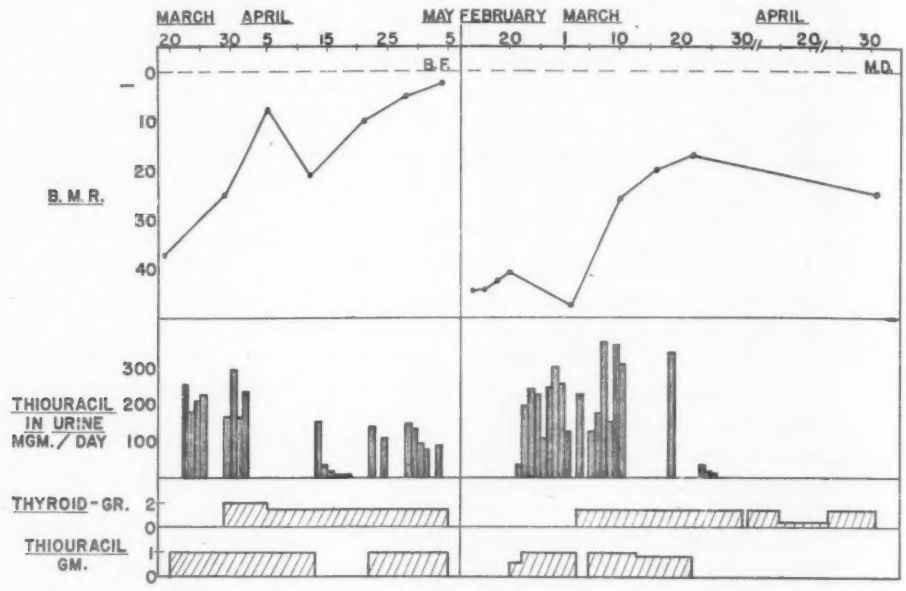

FIGURE 6.

Note that thiouracil had essentially no effect in lowering the metabolic rate of two myxedematous patients and that it did not prevent desiccated thyroid from elevating the rate. Also note the rate of excretion of thiouracil in the urine and the duration of its excretion following cessation of treatment.

Results of Treatment

Although one is interested in observing any and all effects, good or bad, of thiouracil in the treatment of thyrotoxic subjects, most of the attention is centered on the clinical response of the thyrotoxic manifestations, including particularly the amount of gain in weight; the fall in the basal metabolic rate; the changes in the thyroid gland and the changes in the eyes.

In the 9 cases of thyrotoxicosis reported above, there was a distinct clinical improvement beginning only a few days after the treatment with thiouracil was instituted. This was true whether the patient was hospitalized or was carrying on essentially his normal amount of work. Of course, the thiamine,[9] sedatives, reassurance and other such factors played a distinct role in this accomplishment. This improvement increased progressively until the symptoms of thyrotoxicity had essentially disappeared, within four to seven weeks. Gain in weight, a good index to improvement, took place, most rapidly during the fourth and fifth weeks of treatment.

The fall in the metabolic rate was in close accord with the clinical improvement. In almost all cases the metabolic rate did not fluctuate, but fell progressively downward, in some cases going as low as −15 per cent. A normal level was reached as quickly in severe cases as in the milder ones. Once it returned to normal it tended to stay there so long as the thiouracil was continued.

The changes in the thyroid gland were variable. In 3 patients there was definite, but slight, enlargement in the gland during the first two weeks of treatment. Subsequently the glands returned to their original size. In 2 cases the gland became progressively smaller and softer, finally returning to an essentially normal size. In the other 4 cases it became somewhat smaller and softer than it was originally. In this connection it is significant

that in Case 2 the gland became definitely smaller and softer in association with treatment with desiccated thyroid.[10] This method of treatment has a good rationale because it tends to inhibit the excessive production of thyrotropic hormone, thus

A second possible complication consists of renal involvement. Thiouracil is quite insoluble in distilled or tap water, although it is readily soluble at pH 8.5. We have found no crystals in the urine, no albuminuria and no sedimentary changes.

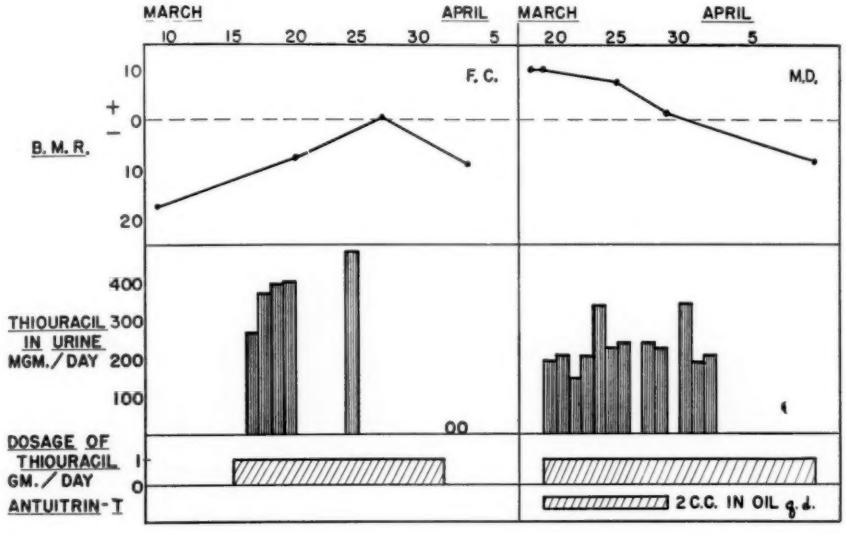

FIGURE 7.

Note that antuitrin-T (thyrotropic hormone) administered with thiouracil caused no elevation in the metabolic rate of a "normal" subject (M. D.). Note also that the treatment of a patient with a large colloid goiter (F. C.) caused no essential change in the metabolic rate. The rate of excretion of thiouracil in the urine should also be observed.

preventing thyroid hyperplasia. We believe that it is partially through this mechanism that desiccated thyroid is of advantage in controlling malignant exophthalmos.[4] For these reasons, we plan to use thyroid, along with thiouracil, after the metabolic rate has remained within a normal range for a few weeks.

The enlargement of the thyroid gland, associated with thiouracil treatment, that occurred in the 3 cases mentioned above, and the increase in the oculopathy in 1, suggest that in human beings, as in animals, thiouracil leads to excess thyrotropic hormone activity.

Complications of Treatment

The most serious complication thus far observed was the agranulocytosis in a case reported by Astwood. However, his patient was receiving 2 gm. of thiouracil daily, a dosage that is now believed to be unnecessarily high. Yet this is a complication that one must bear in mind, even if a smaller dosage is used, because we have found that the bone marrow takes out a relatively high concentration of thiouracil. We made frequent white-cell counts in our cases, but observed no significant drop.

We have found no essential alteration in the daily urine volume nor in the phenolsulfonephthalein excretion. However, 2 patients developed slight pitting edema with elevation in the serum chloride and a slight fall in the carbon-dioxide combining power. These changes disappeared without discontinuation of the drug and apparently led to no ill effects. Nevertheless, the mechanism of the development of these changes is being investigated.

One patient developed swelling and slight tenderness of the submaxillary salivary glands, which subsided after two days in spite of continuation of the drug therapy. There were no complaints of unpleasantness from the taste of the medicine or general effects from it.

In the patient who was pregnant no ill effects were observed. Furthermore, we have found in rats that saturation of these animals with thiouracil did not interfere with the follicularization or the luteinization induced by pregnancy urine.

SUMMARY

Nine unselected cases of thyrotoxicosis have been treated with thiouracil. In each case the

toxic manifestations disappeared and the basal metabolic rate returned to a normal range. Blood-iodine studies, conducted on 4 patients, showed in each case a fall of the protein-bound iodine to a low normal or subnormal level.

Studies have been performed of the blood levels of thiouracil and its excretion in the urine.

No serious complications from the drug have been encountered, but all patients receiving this drug should be carefully followed.

This report deals only with the early changes resulting from treatment with thiouracil. The results of prolonged treatment will be reported at a later date.

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SPINA BIFIDA AND CRANIUM BIFIDUM*

V. The Arnold–Chiari Malformation: A study of 20 cases

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THE Arnold–Chiari malformation is a congenital anomaly of the hindbrain characterized by a downward elongation of the cerebellum and brain stem into the cervical portion of the bony spinal canal. The condition has been considered a rarity and is unknown to a large percentage of the medical profession. The purpose of this study is to present evidence that it is a frequent accompaniment of myelomeningocele and to discuss the clinical and pathological significance of this relation and other associated findings.

Review of Literature

The literature on the malformation is limited. The anomaly was originally described by Arnold[1] in 1894 and by Chiari[2] in 1895. Schwalbe and Gredig[3] published an anatomic and embryologic description of it in 1907, including reference to an earlier study by Solovtzoff.[4]

In 1935, Russell and Donald[5] reported 10 cases of Arnold–Chiari malformation occurring in infants with myelomeningocele. They showed that the anomaly of the cerebellum and medulla in these cases was the prime factor in the production of the complicating hydrocephalus, and suggested that this anomaly might be the mechanism of hydrocephalus in all cases of myelomeningocele and in some cases of simple meningocele.

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Penfield and Coburn[6] in 1938 presented an attractive explanation of the development of the malformation in a case of theirs observed at operation and autopsy. They considered the malformation to be brought about by traction on the brain stem in embryonic life resulting from fixation of the spinal cord at the meningocele site. Normally, growth of the vertebral column and spinal cord occurs at an equal rate until the third month of intrauterine life. After this the bony vertebral canal outstrips the cord in growth, and owing to the anchoring of the cerebrospinal axis by the position of the cerebellum above the foramen magnum, the spinal cord is normally pulled upward so that the conus medullaris comes to lie opposite the first lumbar vertebra. When spina bifida and meningocele are present, the cord may become fixed by herniation and adhesion at the site of the defect so that traction is exerted on the brain stem by the continued growth of the vertebral column and a portion of the hindbrain drawn downward through the foramen magnum. In support of this theory is the observation of Penfield and Coburn that the cerebellar "tails" retracted upward a distance of 3 cm. on being freed from their attachments to the medulla at operation. In their case, and in those of Russell and Donald, the spinal nerve roots in the cervical region were found to pass upward to the intervertebral foramens, rather than horizontally. This was interpreted as additional evidence of a downward traction on the cerebrospinal axis

In 1938, Aring[7] reported a case of cerebellar and brain-stem malformation in an adult with cerebellar symptoms without associated hydrocephalus or meningocele. This resembled the Arnold–Chiari malformation anatomically.

McConnell and Parker[8] in 1938 published a report of 5 cases of hindbrain malformation similar to that described by Arnold and Chiari, but apparently not associated with spina bifida or meningocele. These cases, and that of Aring, tend to cast doubt on the traction theory of the genesis of hindbrain malformation, or else suggest that other mechanisms than traction may be concerned in its production. It is interesting that, in Aring's case and in 4 of the 5 cases of McConnell and Parker, spina bifida occulta was not excluded. X-ray photographs of the spine were apparently taken in only 1 case and in that one only the lumbar spine was studied and found normal.

In this same report McConnell and Parker described autopsies on 6 infants with myelomeningoceles, 4 of whom had the Arnold–Chiari malformation. In the other 2 there was a "prolongation of flattened cerebellar tonsils through the foramen magnum associated with a nodule on the dorsal surface of the medulla."

D'Errico[9] in 1939 discussed the surgical treatment of hydrocephalus associated with spina bifida and emphasized the importance of the Arnold–Chiari malformation in the production of hydrocephalus in such cases. He reported 10 cases of myelomeningocele, all of which had an associated Arnold–Chiari malformation.

Two cases were reported by Adams, Schatzki and Scoville[10] in 1941. One of these was associated with myelomeningocele. The other case was similar to those of McConnell and Parker, and x-ray films of the entire spine failed to show spina bifida.

In 1941, List[11] included the Arnold–Chiari malformation in an extensive discussion of the neurologic syndromes accompanying bony developmental defects in the occipital region.

Ogryzlo[12] presented 7 cases in 1942. Of these, 3 were associated with myelomeningoceles, and 1 with simple meningocele, whereas the remaining 3 had no overt spina bifida. Again spina bifida occulta was apparently not excluded.

TABLE 1. *Data on 20 Cases of Arnold–Chiari Malformation.*

CASE NO.	AGE	SEX	TYPE OF HYDROCEPHALUS	CRANIO-LACUNIA	MICRO-GYRIA	MYELOMEN-INGOCELE	HYDRO-MYELIA	DIPLO-MYELIA	BASIOCCIPI-TAL DEFECT	
240161	1½ yr.	M	Block of 4th ventricle	+	+	+	0	+	+	
248459	4 mo.	M	Communicating	+	+	+	+	+	0	
249537	5 wk.	F	Not determined	+	+	+	0	0	+	
246581	7 wk.	F	Block of 4th ventricle	+	+	+	0	0	0	
23804	11 mo.	F	Communicating	+	+	+	+	0	0	
234581	4 mo.	M	Communicating	+	+	+	+	0	+	
22230	8 mo.	F	Communicating	+	+	+	+	0	+	
189446	5 mo.	M	Communicating	?	+	+	+	0	0	
161359	3 days	F	Communicating	?	+	+	+	0	?	
158560	3 mo.	M	Communicating	?	+	+	+	0	?	
17675	10 mo.	M	Communicating	?	+	+	+	0	?	
17621	1 mo.	F	Not determined	+	+	+	0	0	0	
149346	4 mo.	F	Block of 4th ventricle	+	+	+	0	0	0	
16125	2 days	F	Not determined	+	+	+	0	0	?	
15337	7 days	F	Not determined	?	+	+	?	0	+	(Klippel–Feil deformity)
239648	4 days	F	Communicating	+	+	+	?	?	0	
245878	3 mo.	M	Communicating	+	?	+	?	?	0	
252151	9½ mo.	M	Block of 4th ventricle	+	+	+	0	0	+	(platybasia)
255224	8 mo.	M	Communicating	+	+	+	?	+	+	(platybasia)
267425	6 days	F	Communicating	+	+	+	?	?	0	

REPORTED CASES

Twenty consecutive cases of Arnold–Chiari malformation that came under observation at the Children's Hospital from 1929 to 1943 were examined. Nineteen of these were studied at autopsy as well as clinically. Their principal clinical and anatomical features are presented in Table 1. All these patients were infants between two days and eighteen months of age. Meningocele, with or without hydrocephalus, was the reason for hospitalization in each case.

The malformation of the cerebellum and medulla in these 20 cases was anatomically identical with Arnold's original case and with those of Russell and Donald. Two parallel tongue-like processes from the inferior poles of the cerebellar hemispheres extended downward through the foramen magnum and were closely applied to the posterior surface of the medulla (Fig. 1). In each case from one half to two thirds of the medulla lay below the level of the foramen magnum. The

medulla was somewhat elongated, slightly narrower than usual and flattened anteroposteriorly.

As pointed out by Russell and Donald, the cerebellum was hypoplastic and in most cases lacked differentiation into vermis and lateral lobes. The tail-like prolongations seemed to originate from

FIGURE 1. *Sagittal Section through the Cerebellum and Brain Stem in a Typical Case of Arnold–Chiari Malformation.*

the whole inferior pole of the cerebellum, and in sagittal section appeared to pass down from the nodulus. Microscopic examination of the cerebellar tails shows simply hypoplastic tissue with preservation of the usual cortical architecture.

The fourth ventricle was elongated and flattened. Its lumen was almost obliterated in many cases by the close approximation of the cerebellar "tongue" to the posterior medulla. The foramens of Magendie and Luschka lay below the level of the foramen magnum and were usually identified with difficulty.

In 2 of the cases there was a nodule on the dorsal surface of the medulla, located in the midline and lying just ventral to the lower extremities of the tail-like cerebellar prolongations, or immediately caudal to these. Sagittal sections through the medulla at this point showed this nodule to represent an exaggeration of the normal structural relations of the most caudal extremity of the fourth ventricle, with an overlapping of the upper cervical cord segment by the adjacent medulla.

The choroid plexus lay in the midline on the ventral surface of the cerebellar prolongations, as a rule, and extended down to their caudal ends. The pia-arachnoid was thickened and extremely vascular over the cerebellar tails, and tended to obscure them in the undissected specimen.

The upper cervical nerve roots were found to run upward to the intervertebral foramens in these cases, just as in those of Russell and Donald and that of Penfield and Coburn (Fig. 2).

Myelomeningocele

Spina bifida and myelomeningocele were present in each of the 20 cases of Arnold–Chiari malformation examined. Usually these were large herniations with extensive neural involvement. In the few that were dissected out post mortem and in all those excised ante mortem there were dense fibrous adhesions binding the lumbar myelomeningocele sac to the margins of the defect in the vertebral arches. Frequently the lumbar nerve roots were incorporated in these adhesions.

Hydrocephalus

Internal hydrocephalus was present in each of the 20 cases of hind-brain malformation. Twelve cases were of the communicating type. In 4 there was obliteration of the fourth ventricle by squeezing of the medulla and cerebellar tails into the narrow confines of the cervical spinal canal. In the remaining 4 cases the type of obstruction was not determined post mortem and no definite conclusion could be reached by re-examination of the fixed brain.

From the work of Russell and Donald and from the examination of the brains in this series it appears that hydrocephalus may be produced by the Arnold–Chiari malformation in several ways: First, the fourth ventricle or the foramens of Luschka and Magendie may be mechanically obstructed by the squeezing of the medulla and cerebellar tails into the narrow cervical spinal canal. Obstructive hydrocephalus results. Secondly, with less severe traction and constriction the relatively unsupported subarachnoid space may be obliterated at the level of the foramen magnum by pressure of the herniated hindbrain, whereas the fourth ventricle remains patent. The foramens of Magendie and Luschka come to lie below the level of the foramen magnum, allowing free passage of fluid to the spinal subarachnoid space, but no egress from the latter to that of the posterior fossa is possible because of the block at the fora-

men magnum. Communicating hydrocephalus results. Thirdly, owing to the traction on the brain stem there may be mechanical irritation of the arachnoid of the basal cisterns with the production of an aseptic inflammation and plastic exudate that block passage of fluid from the spinal to the cerebral subarachnoid space.

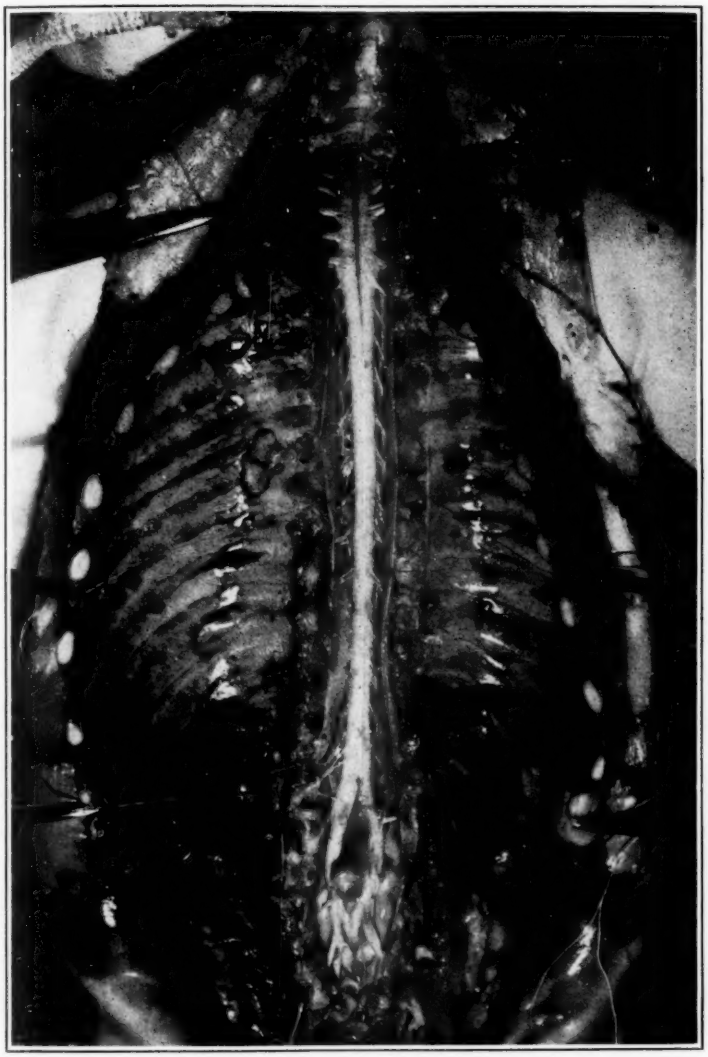

FIGURE 2. *Anterior View of the Spinal Cord at Autopsy in a Case of Arnold–Chiari Malformation.*

Note the upward course of the cervical nerves and the lumbar diplomyelia. The myelomeningocele was located in the lumbar region.

Microgyria and Craniolacunia

Two findings that have not been described previously in the literature as occurring with the Arnold–Chiari malformation are microgyria and craniolacunia. In all 20 cases examined there was conspicuous microgyria. The cerebral gyri were distinctly smaller than usual, and more numerous. "Wormy" is the most descriptive term for these small convolutions.

The exact nature of microgyria of the diffuse cortical type is not well understood, nor is its relation, if any, to the Arnold–Chiari malformation clear. The fact that it was present in each case examined, however, seems worthy of comment.

Craniolacunia, or, as it has been called, caput fenestratum, lacunar skull or *Lückenschädel*, was present in 15 of the cases examined. Its absence in the other 5 cases is subject to question, as it is easily missed at routine post-mortem examina-

tion; this is particularly true if the observer is not familiar with the condition.

Craniolacunia is characterized by a diffuse involvement of the whole skull with rounded defects of varying size in one or both tables, separated by bony ridges. The defects may be wholly devoid of bone. A study of craniolacunia from the roentgenologic point of view has been recently made by Vogt and Wyatt.[13] These authors found craniolacunia present in 52 (43 per cent) of 120 patients with meningocele and discovered that it was more frequently found with myelomeningocele than with simple meningocele.

The etiology of craniolacunia remains obscure. Theories concerning its relation to increased intracranial pressure are unproved. Vogt and Wyatt considered it to be an unfavorable prognostic sign in meningocele cases. Whatever its significance may be, its high incidence in Arnold–Chiari malformation seems deserving of notice.

Other Findings

Hydromyelia was present in 8 cases. In each of these the coexisting hydrocephalus was of the communicating type. This relation seems significant as regards the genesis of the dilated central canal.

Bony defects of mild degree in the basiocciput were present in 4 cases, and one of these had, in addition, spina bifida of the atlas. Three cases showed a definite degree of platybasia. In another case there was fusion of the cervical vertebras suggestive of the Klippel–Feil deformity. These bony anomalies of the base of the skull and cervical vertebras are apparently not of uncommon occurrence with the Arnold–Chiari malformation, but no developmental relation between the two types of defect has been established.

Three of the cases had diplomyelia, or reduplication of the spinal cord. In all cases the lower thoracic and lumbar regions were involved. Herren and Edwards[14] have recently made an exhaustive study of this anomaly, which they believe represents a certain degree of twinning (Fig. 2).

Discussion

From the study of these 20 cases of the Arnold–Chiari malformation and those reported in the literature there is a striking relation between the hindbrain malformation and low dorsal and lumbar myelomeningoceles. These findings suggest that a high proportion of infants with myelomeningoceles seen clinically may be expected to have a coexisting Arnold–Chiari malformation. An analysis was made of 297 cases of myelomeningocele studied at the Children's Hospital between 1929 and 1942. Of these, 5 came to surgical exploration of the posterior fossa, and 3 of these were later autopsied. In addition, 15 other cases that did not have cerebellar exploration were examined post mortem. In all 20 cases the Arnold–Chiari malformation was present.

The association of the hind-brain malformation with myelomeningocele, as opposed to simple meningocele, seems to be particularly significant in the light of the traction theory of genesis of this anomaly. A large myelomeningocele is likelier to produce fixation of the cord at the site of the spina bifida than is a simple meningocele, or a meningocele sac containing only a few strands of neural tissue. Hence, if the traction theory is valid, the Arnold–Chiari malformation would be expected to occur far more often with large myelomeningoceles than with simple meningeal herniations.

The cases reported in the literature, as well as those under discussion, offer substantiation of this concept.

Although in all the cases reported the protrusion was low dorsal, lumbar or lumbosacral, it is probable that the same mechanism produces a similar but less marked degree of the same anomalous development in upper dorsal and cervical protrusions. Until this condition is produced experimentally, it is not safe to conclude that the traction theory gives the complete explanation of this phenomenon. The microgyria, craniolacunia and other associated anomalies suggest that there is a basic widespread defect. From the information at hand one must conclude that the combination of myelomeningocele, craniolacunia, microgyria and Arnold–Chiari malformation constitutes a clinical entity. It is possible that the easily demonstrable radiographic changes of craniolacunia will provide a simple clue to the diagnosis.

The preoperative recognition of the syndrome is of great importance in planning a surgical attack on the problem. The long-time results of surgical treatment have not been encouraging, but in properly selected cases surgery is definitely indicated. One should not be misled by a short follow-up in these patients, who may do extremely well for a few months or even years and then suffer from recurrent block in circulation of the cerebrospinal fluid. The history of Penfield's[6] adult patient provides striking proof that the presence of the Arnold–Chiari malformation does not necessarily interfere with full use of the extremities and mental competence. This patient's circulation of cerebrospinal fluid was presumably in a marginal but satisfactory state of balance for many years and might have remained so except for a slight shift in pressure, which promptly created a vicious circle.

Obviously, surgical treatment should be limited to the patients without extensive paralysis of the lower extremities and sphincters. It should not be offered if hydrocephalus is so advanced that it is inconsistent with normal mental development. dinarily follows in ten days to two weeks. If increased intracranial pressure is a problem in this interval, it can easily be controlled by continuous ventricular drainage. In favor of reversing the order of the two procedures is the fact that the

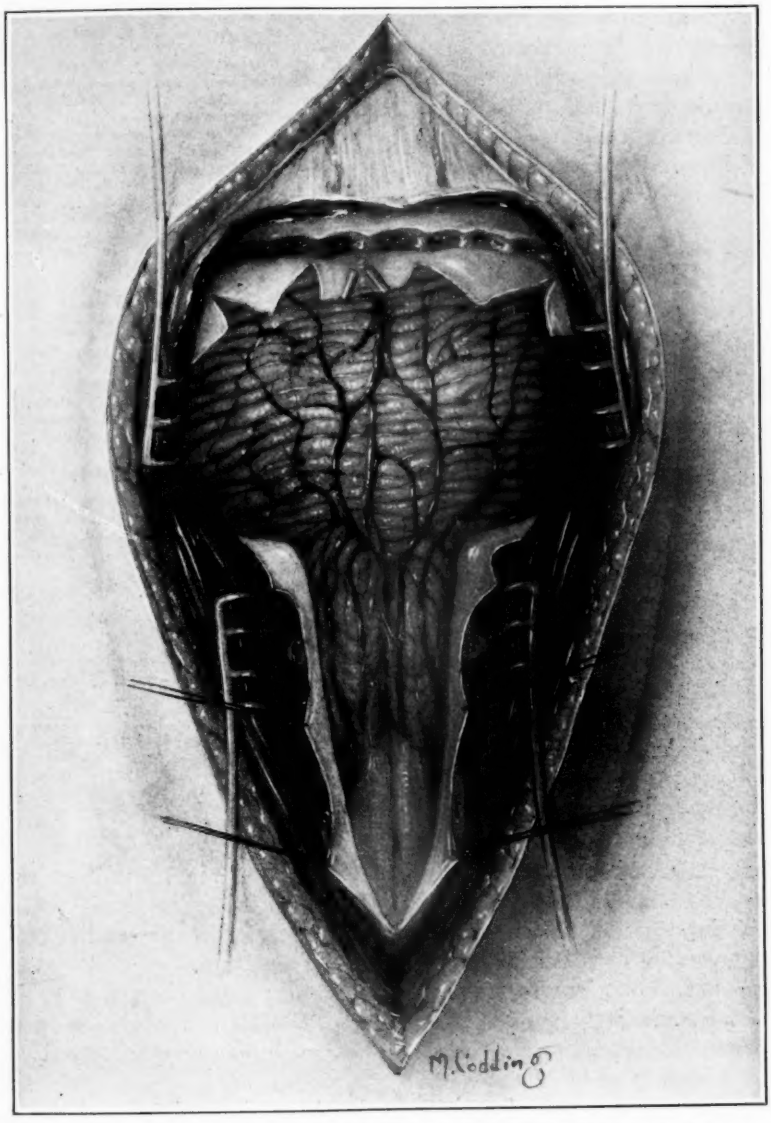

FIGURE 3. *The Arnold–Chiari Malformation as Exposed during Exploration of the Posterior Fossa.*

The exact management of the surgical problem must depend on the particular features of the individual case. In general it has seemed to us more satisfactory to excise the meningocele as the first step, freeing the tissues as thoroughly as can be done without damage to functioning nerve tissue. This usually means only a slight increase in mobility of the spinal cord. The findings at this operation occasionally deter one from carrying out exploration of the posterior fossa, which or- pressure may remain normal following the cerebellar exploration, thus simplifying the management of the meningocele.

In the exploration of the posterior fossa, which can be carried out by a simple midline incision, the essential feature is a wide decompression, including removal of the occipital bone down through the foramen magnum and laminectomy of the upper cervical vertebras, continuing down until the cord is exposed and the cerebellar tails are

freed (Fig. 3). This is not a particularly formidable procedure if carried out with due respect for the anomalous venous channels usually present in the dura.

It is hoped that in the future we may be able to select more certainly those patients who should be subjected to this operative procedure. Although it is possible to demonstrate the malformation by air injection, it has not been satisfactory to date to use this method to distinguish the promising from the hopeless cases. Electroencephalography holds definite promise of identifying the associated microgyria, which is probably a contraindication to operation.

Summary

Twenty cases of the Arnold–Chiari malformation associated with myelomeningocele have been studied, and the literature has been briefly reviewed.

The anomalous development has been strikingly similar in all cases.

The majority of the patients had associated microgyria and craniolacunia.

The outlook is poor in most cases, but promising cases should be carefully selected and subjected to surgical treatment.

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MEDICAL PROGRESS

THE MODIFICATION OF INTESTINAL MOTILITY BY DRUGS*

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BOSTON

ALTHOUGH the effect of drugs on intestinal motility is an ancient and well-worn subject of investigation, it is only within relatively recent times that observations have been carried out on untraumatized intestinal loops of normal animals and of man. In such experiments, the artefacts and abnormal responses that attend anesthesia, decapitation, shock and local trauma of the bowels are eliminated, and a truer picture of motility, both in the normal state and as influenced by drugs, is obtained. Procedures using intact intestinal loops are not designed to differentiate the function of longitudinal and circular muscles or to answer similar questions of basic physiologic interest. In evaluating the total effect of a drug on human intestinal motility, however, results of investigations using the intact bowel, particularly the bowel of man, are of paramount significance. For this reason, emphasis will be placed, whenever possible, on the results obtained from human experimentation.

Even if intact bowel loops in one species are used, considerable variation in the intestinal reaction to drugs can be observed, depending on such factors as the dose and route of administration of the drug, the activity and the content of the intestine at the time of the experiment and the technic used in recording motility. In interpreting the results of any pharmacologic study of intestinal motility, it is therefore necessary to take these factors into account. In particular, the advantages, disadvantages and properties of different technics must be understood before apparently contradictory observations can be correlated.

Five general methods are used in recording the motor activity of the bowels in situ. These are direct observation, roentgenologic and fluoroscopic studies, kymographic recording by balloons, re-

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cording by devices attached to smooth-muscle groups, and recording of intraenteric pressures.

Direct observation (O).* The intestinal movements may be observed with the naked eye or by photographic means. Usually the intestinal loops are surgically exposed, but occasionally the intestinal activity within a thin-walled hernial sac may be studied. The method eliminates nonphysiologic stimuli within the bowel, but external stimuli resulting from surgical exposure are not excluded. The greatest disadvantage of this technic arises from the fact that the complexity of intestinal movements makes accurate interpretation extremely difficult.

Roentgenologic and fluoroscopic studies (X). With this method, the normal physiology of the intestinal tract is least disturbed, although the question may be raised whether the bowel handles the barium suspension in a manner similar to its handling of foodstuffs. On the other hand, this method merely shows the end result of several interacting forces that may or may not give an indication of the motility of the organ under investigation. For example, the rate of gastric emptying, which is often used as a criterion of the stomach's motor activity, may be delayed by high intraduodenal pressures as well as by gastric atony.

Kymographic recording by balloons (B). Balloons can be inserted within a hollow viscus and its contractions recorded kymographically by various means. A balloon method free of objectionable features has yet to be devised, since the presence of the balloon in the intestines serves as a constant and abnormal source of stimulation. Furthermore, balloons occasion more or less intestinal obstruction, are nondispersible boluses in organs that for the most part transport dispersible liquids, and are subject to a variety of influences besides those of local muscular contraction. Nevertheless, the fact that the balloon method lends itself to graphic recording is a tremendous advantage, and if used with due consideration of its limitation, this method yields important results. Balloons can be inserted in intestinal loops that have been opened by surgical means, or they can be used in the intact bowel of man by the Miller–Abbott technic of intestinal intubation.

Recording by devices attached to smooth-muscle groups (M). In surgically exposed loops of bowel, recording devices can be attached to muscle groups of varying size and extent. This technic is precise and allows the action of longitudinal and circular muscles to be differentiated. On the other hand, it requires surgical procedures and by itself gives no indication of the forces within the bowel.

Recording of intraenteric pressures (P). This method has been attempted by only a few investigators[1, 2] and no complete pharmacologic studies have yet been carried out by this method. Before the full picture of a drug's effect on intestinal motility can be drawn, however, its effect on intraluminal pressures as well as on muscular activity and transport of contents must be studied.

*This and the other four symbols denote the method employed in the experiments cited

Not only method but phraseology has suffered from lack of standardization. In order to avoid confusion, the following definitions of terms used in this review are given:

Transport. The advance of intestinal contents, whether chyme, barium, balloons or other material, is referred to as transport.

Tone. The tone of the intestine is considered to be the caliber that it maintains in the face of a distending force. This force may vary considerably depending on the method of investigation.

Waves. A tremendous number of terms have been used to describe the wave patterns created by intestinal motility. The most desirable terminology is one that labels waves with letters or numerals and avoids the implication that wave patterns and their effect on transport are identical. Unfortunately, this terminology is limited to methods employing graphic recording. In this review, which includes material obtained by nongraphic methods, wave patterns will be divided into "propulsive" and "mixing" types. Under the heading of propulsive waves fall such terms as "peristaltic waves," "mass peristalsis," "Type II waves" of the colon[3] and "L waves" of the small intestines,[4] whereas mixing waves include "rhythmic segmentation," "Type I waves" of the colon and "S waves" of the small intestine. The adjectives "propulsive" and "mixing," as used here, describe wave patterns and do not necessarily indicate propulsion or mixing of intestinal contents. Thus, under certain conditions, no transport may occur even when propulsive waves are in evidence, and vice versa, chyme may flow downstream when only mixing waves are present.

Motility. This term, often used incorrectly as synonymous with "transport," refers to the total spontaneous muscular activity of the intestine. The three component parts of motility — tone, propulsive waves and mixing waves — interact to exert a certain force on the intestinal

contents. Actual transport, however, depends not only on the forces created in any one intestinal area but also on the motility and intraluminal pressures of adjoining areas. As a general rule, a low tone and frequent propulsive waves of large amplitude are conducive to transport, whereas a high tone, which eliminates effective "diastole" between waves,[5] or a low tone with absent propulsive waves, or inco-ordination of adjoining intestinal segments,[3] retards transport. In many reports, motility is called propulsive or nonpropulsive depending on its effect on transport.

General Effects of Drugs

When the intestine is subjected to a pharmacologic action, tone, propulsive waves and mixing waves may be uniformly affected, or the drug may act predominantly on any one of these factors. If this important concept is kept in mind, many apparent contradictory pharmacologic effects will be explained. Thus, a drug may stimulate motility by inducing a marked spasm — that is, high tone — but for reasons given above, it will decrease transport. Vice versa, a drug may decrease motility by reducing both tone and wave activity, but if the major effect of the drug is on tone, transport of intestinal contents may be increased. Quite apart from their specific effect on intestinal motility, drugs may influence transport in other ways. If transport is inhibited because an uncoordinated motility obtains in two adjoining intestinal areas, exhibition of a drug may co-ordinate motility and facilitate transport regardless of the specific action of the drug. Another possible factor, about which little is known, is the effect of drugs on the quality and quantity of intestinal secretions and on the speed of absorption. If these are changed, intraintestinal pressures vary accordingly, even if motility is constant, and the rate of transport may be altered. Considerations such as these show why it is most difficult to determine the actions of a drug merely by observing its effect on intestinal transport.

Drugs may influence intestinal motility through a variety of routes. Some affect the irritability of the musculature directly. Others mimic, enhance or inhibit the action of the humeral agents that are believed to transmit impulses from the nervous end organs to the effector cells. As a rule, drugs that favor the transmission of cholinergic (parasympathetic) impulses stimulate motility, whereas drugs that favor the transmission of adrenergic (sympathetic) impulses depress motility. The supposedly reversed effect of these agents on the intestinal sphincters plays a very minor role in controlling transport of intestinal contents. Quigley and his associates[6] have shown, for instance, that gastroduodenal pressure gradients, which reflect gastroduodenal motility, are of more importance in controlling gastric emptying than is an independent action of the pyloric sphincter (P).

Drugs Retarding Transport

Morphine

The confusion and contradiction concerning the action of morphine and its related alkaloids on intestinal motility have gradually been cleared away during the past decade. Much of the credit for this achievement belongs to Quigley, Highstone and Ivy,[7] who urged that propulsive be distinguished from nonpropulsive motility, and to Abbott and Pendergrass,[5] who demonstrated the feasibility of using the intact small bowel of normal man for pharmacologic studies.

When clinical doses of morphine are injected subcutaneously, a marked rise in tone involves the whole intestinal tract within a few minutes. In the human duodenum, the increase in tone is of sufficient intensity to obliterate the lumen (B and X).[5] Concomitant with this tonal spasm, the amplitude of the mixing waves is decreased but their frequency is increased; whereas propulsive waves are completely abolished, partly because of the high tone that prevents diastolic relaxation. Similar but less prompt and striking changes occur in the jejunum and ileum. Except for an initial spurt caused by the rising tone, transport is almost completely abolished. The characteristic duodenal spasm that follows the administration of morphine may, in fact, reverse the direction of transport and may play a part in the nausea that at times attends this drug's exhibition (B and X).[8]

After a period of about thirty minutes, the tone of the small intestine drops to a low level and remains depressed for four hours or even longer.[5] Propulsive waves continue to be absent. As a result, transport, which is initially delayed by spasm, is subsequently delayed by atony.

The response to morphine of the human ileum at or near an ileostomy is also characterized by an increase in tone, increased frequency of mixing waves (M)[9] and a decrease in propulsive motility (B).[10] In these cases the effect of morphine is more pronounced, and the increase in tone of longer duration (two to three hours), than is found to be the case in the normal intact ileum.[5] An ileostomy may, however, considerably alter ileal function, as may the disease for which the ileostomy is performed. Hence, the observations made on the intact viscus are probably more indicative of the small bowel's response to morphine.

The careful studies (B) of Adler, Atkinson and Ivy[10, 11] show that the colon of both man and the

dog react to morphine in roughly the same fashion as does the small bowel. Nonpropulsive motility — that is, the tone and the amplitude of mixing waves — is increased, but propulsive motility is strikingly diminished. In the colon, however, the elevated tone persists for two to three hours. Whether a late fall in tone ever occurs has not been reported.

Animal experimentation in recent years has yielded consistent results in that morphine is generally found to have a stimulating effect on intestinal motility, but in other respects the observations are more variable. It is, for instance, recorded that morphine abolishes peristaltic waves (B),[12] increases the amplitude of peristaltic contractions (B),[13] and produces intermittently recurring tonus waves (O).[14]

Human experimentation is not invariably attended by consistent results,[10] and at times some areas in the colon may be relaxed while the greater part of this organ is exhibiting a high degree of nonpropulsive motor activity (B).[15] Nevertheless, the evidence is unequivocal that in man morphine usually increases tone and decreases propulsive motility. In the small intestine, a period of atony succeeds the period of hypertonicity. Whether spasm, atony or lack of segmental co-ordination obtains, however, the result is the same: transport of intestinal gas and chyme is seriously retarded.

The clinical application of these facts is clear. Unless morphine is needed for its unsurpassed analgesic action, it should not be used in treating nausea and vomiting, conditions in which intestinal transport is already seriously deranged. Nor, contrary to some opinion, is morphine to be used for the express purpose of treating or preventing paralytic ileus. In patients with partial mechanical obstruction, morphine may relieve pain by abolishing the marked fluctuations in intraenteric pressures produced by huge propulsive waves, and the initial increase in tone may elevate the basal intraenteric pressure (P),[2] but expulsion of the trapped contents will not be furthered. In this connection, it may be added that the duodenal spasm that attends the use of morphine often makes therapeutic intubation of the small intestine very difficult. If possible, therefore, intubation should be attempted before heavy doses of morphine are given.

Heroin, Dilaudid, Pantopon, apomorphine and codeine have the same qualitative effect on intestinal motility as does morphine (X)[16] (B).[13, 17, 18] The action of codeine and apomorphine is relatively weak, whereas 1 to 2 mg. of Dilaudid produces the same results as does 8 to 10 mg. of morphine (B).[10]

Papaverine, unlike the other opium alkaloids, is known to inhibit motility. In man, its intravenous injection usually reduces the tone of the colon (B),[18] but most studies on the intestinal effects of this drug have been confined to excised intestinal strips.*

Adrenalin

Intestinal motility should theoretically be inhibited by adrenalin or other sympathomimetic drugs and by drugs that antagonize the action of cholinergic nerves. The use of adrenalin for this purpose is unfortunately of little avail. In the first place, the results obtained with adrenalin are often variable and unpredictable. Not infrequently it has been reported to exert a stimulating effect on motility, most recently by Wells et al.,[19] who noted that intra-arterial injections of adrenalin increased the circular contractions in the distal colon of animals (B and M). In other loops of the dog's colon (B),[20] and in the small intestines of dogs (B)[21] and man (O),[22] the reaction is more what one would expect, in that a constant intravenous injection of adrenalin causes a decrease in tone and an inhibition of wave activity. After a period of two to three minutes, however, intestinal motility breaks through this inhibiting effect, even though the injection rate of the adrenalin is accelerated.

Although subcutaneous injections of adrenalin have at times induced relaxation in the human bowel (B),[23] no clear-cut or consistent effects are usually observed. This is true of the intact human small intestine (B)[24] as well as other preparations. The usual explanation advanced for the inability of adrenalin to effect intestinal motility is that clinical doses that might be effective elicit marked cardiovascular responses.[25] Youmans,[26, 27] however, has shown that the dog's intestine (B), particularly if sensitized by denervation,[28] responds to intravenous adrenalin in amounts that are less than the minimal pressor dose. Hence, the variable response of intestinal motility to subcutaneous administration of adrenalin may be partly due to the bowel's tendency to escape from the influence of a constant supply of this drug.

Amphetamine

The search for a sympathomimetic amine that specifically inhibits intestinal motility has not yet borne fruit. Some hope was held for amphetamine (Benzedrine) because it appeared to relax spasm and enlarge the lumen of the small and the

*Batterman,[72] in studying the actions of the synthetic substance 1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester hydrochloride (Demerol), finds that human intestinal motility is depressed by this drug. A review of the literature by Batterman and Himmelsbach[72] reveals, however, that this spasmolytic effect is not always obtained.

large bowel (X).[29] This observation was partially confirmed (X)[30] and also contradicted (X).[31] Balloon records of the human small intestine show that if any response attends the exhibition of amphetamine sulfate (15 to 20 mg.), this response tends to consist of a moderate reduction of tone and wave activity (B).[32] In half the cases, however, motility is unaltered. The reactions of the human colon are no less equivocal; only occasionally is tone depressed and the amplitude of propulsive waves lessened (B).[15, 32, 33] Local application of a 0.5 per cent solution of amphetamine sulfate to the human rectal mucosa, examined by means of a proctoscope, is also without motor effect.[35]

Atropine

Atropine, when used in clinical doses, depresses all phases of intestinal motility. On this point, almost all recent studies concur, whether carried out in dogs (B)[11, 36, 37] or in man (M),[9] (O),[22] (B)[33] and (B and X).[38] Although the efficacy of atropine in inhibiting intestinal motility varies with the dose, 0.6 mg., given subcutaneously, is usually sufficient to lower tone, abolish propulsive waves and decrease the amplitude of mixing waves in the small bowel of man (B and X).[38] In the human colon, similar results are obtained with 0.75 mg. (B).[15, 33] Interestingly enough, the effects of atropine are more marked in the distal than in the proximal colon of the dog (B).[11] From the fact that the uniformly depressed tone is unrelieved by propulsive waves, it can be deduced that transport is markedly retarded by atropine.

Following subcutaneous injection, the effects of atropine take place in fifteen to thirty minutes and persist for one to two hours. Intravenous administration of the drug elicits more marked effects of more rapid onset; oral administration produces less pronounced changes in thirty to forty-five minutes.

The question may legitimately be raised why atropine, which is such an effective antispasmodic in experimental studies, is often a source of disappointment in clinical use. Two observations may offer a partial answer. It has been known for some time that atropine effectively abolishes a response to injected acetylcholine, but that it is much less effective in counteracting vagal stimulation. Recently this phenomenon has been quantitated in animals with regard to the pelvic nerve (B and M).[19] Whereas atropine inhibited 97.5 per cent of the stimulating effect on colonic motility of intra-arterially injected acetylcholine, it inhibited only 88.6 per cent of the effect produced by stimulating the pelvic nerve electrically. The usual explanation advanced to account for this discrepancy is that atropine can act to inhibit acetylcholine on cell surfaces, but cannot act on acetylcholine released by nerve fibers, which may end within the cell.[34] The problem has, however, been examined further by Youmans and his collaborators[35] who have presented evidence that atropine inhibits intestinal motility in amounts less than that needed to inhibit the intestinal vagus (B). On the basis of this and related evidence, they suggest that the motor activity of the intestines is maintained at a basal level by acetylcholine produced by the myenteric plexuses, and that this basal function operates in the absence of stimulation by extrinsic nerves. The administration of atropine, according to this concept, makes the intestinal musculature unresponsive to acetylcholine produced at basal levels but has less effect on the humeral agents released by the extrinsic nerves. If this is the case, one can understand why atropine shows to such good advantage in experimental studies attempted at basal levels, whereas in functional or organic abnormalities of the intestine, in which the extrinsic nerves may play an important role, the results of atropinization are less favorable. On the other hand, the hypermotility of the rectosigmoid that at times follows prevertebral ganglionectomy in dogs is inhibited by intravenous atropine (B).[39]

The efficacy of an antispasmodic can be tested under other than basal conditions by observing its action on the intestine rendered spastic by a previous or simultaneous injection of morphine.[15] That the hypermotility produced by morphine is in any way analogous to the hypermotility seen in intestinal disorders has not been proved, although one school of thought holds that the action of morphine on the bowel is essentially cholinergic.[40]

To a certain extent, the action of morphine and that of atropine on intestinal motility are antagonistic. In the dog, small doses (1 mg.) of atropine decrease the transient propulsive motility that occurs after a sizable dose (16 mg.) of morphine is given, but the increase in tone and in mixing waves is not affected. Both the propulsive and nonpropulsive motility stimulated by smaller doses of morphine are, however, antagonized by 1 mg. of atropine (B).[11, 12] If these results are applied to man, it is seen that toxic doses of atropine would have to be used to abolish the spasmodic effect of clinical doses of morphine. Actual experiment bears out this assumption: 0.7 mg. of atropine sulfate only partially inhibits the spasm produced by 8 mg. of morphine (B).[15] Since both atropine and morphine inhibit transport, it is understandable that this effect should be pronounced when both drugs are exhibited together.

Atropine Substitutes

A number of compounds have been synthesized that appear to inhibit intestinal motility without provoking the side reactions characteristic of atropine. Three of these compounds are in quite extensive clinical use: novatropine, Syntropan, and Trasentin. Methylatropine nitrate (Eumydrin) has also been used, especially in the treatment of hypertrophic pyloric stenosis; but although its effectiveness equals that of atropine, its toxicity, at least in mice, is three times as great (M).[41]

Pharmacologically and in its effect on the dogs' intestinal motility, novatropine closely resembles atropine (B).[37] Trasentin produces a moderate reduction of the colonic tone in man and decreases the frequency and irregularity of propulsive waves (B).[15] It appears to be more effective in this respect than is Syntropan (B).[15, 33] The problem deserves further study, however, especially since in most investigations Trasentin has been used in an injectable form, a preparation that the manufacturers have discontinued because of its instability.

Syntropan and Trasentin, unlike novatropine, are said to exert a direct muscle-depressing action as well as an atropine-like inhibition of cholinergic impulses (B).[42, 43] In view of this fact, one might suppose that these compounds could inhibit the motor effects of morphine more successfully than does atropine. Although this expectation was realized for Syntropan in the case of the dog (B),[44] Trasentin was found to be not quite so effective as atropine in reducing morphine-induced hypertonus (B).[15] There is also evidence that morphine and Trasentin should not be used concurrently,[15] although this combination exerts no noxious effects on respiration in the dog.[45]

Drugs Accelerating Transport

Prostigmine

Intestinal motility is theoretically stimulated by acetylcholine or its esters, by drugs that inhibit the activity of cholinesterase and by those that antagonize the action of the adrenergic nerves. The most satisfactory drug for this purpose is undoubtedly Prostigmine, which, like physostigmine, inhibits cholinesterase. Unlike physostigmine, however, Prostigmine is practically devoid of any unpleasant side reactions.

When 0.5 mg. of Prostigmine is given subcutaneously the intact human small intestine responds with a moderate increase in tone and in the frequency and amplitude of the propulsive waves (B).[24] In patients with stomas of the large and the small bowel, a similar stimulation of motility is observed (B).[46, 47] In dogs, the effect is more pronounced in the colon than in the jejunum (B).[46] Since propulsive motility is augmented (B),[47] transport is promoted. One may conclude that in the small and especially in the large bowel, Prostigmine prevents areas of atony, stimulates propulsive waves and co-ordinates these two components of intestinal motility to facilitate transport and expulsion of intestinal contents. Little wonder, then, that Prostigmine is the drug of choice in combating ileus or other conditions where a functional derangement of intestinal transport exists.

Prostigmine Methylsulfate, like atropine, is rather slow in taking effect. A definite change in intestinal motility may not take place until ten to thirty minutes after its intramuscular injection. When Prostigmine Bromide is given orally, its effect may not be noticeable for two to four hours.[47]

Schwartz and his co-workers[46] believe that Prostigmine must exert a direct stimulating effect on intestinal smooth muscle as well as inhibit cholinesterase, because this drug is effective in certain diseases of the digestive tract in which inflammation or anoxia of the intestinal tissues conceivably might impair the humoral transmission of nerve impulses. In support of this belief, they have shown in dogs that repeated intravenous injections of Prostigmine bring about a slight increase in motility even when the animal is atropinized. It is not generally held, however, that Prostigmine has any direct action on the enteric musculature.[48] In well-established cases of sprue, for example, in which the myenteric nervous system is thought to be damaged, Prostigmine in 0.5-mg. doses may produce no change in the motility of the atonic small bowel (B).[49]

Ergotamine

Ergotamine is generally supposed to block adrenergic excitatory effects specifically.[50] Darrow,[51] on the other hand, holds that ergotamine primarily blocks the adrenergic inhibitory effects by "a protection of parasympathetic activity or a physostigmine-like action." This theory is particularly germane to the important work done by Adler, Atkinson and Ivy[47] on the supplementary action of drugs that stimulate intestinal motility (B). These authors found that small doses of ergotamine have no effect on motility of the human colon, but that ergotamine and Prostigmine potentiate each other markedly. If 0.25 mg. of ergotamine is injected with 0.25 mg. of Prostigmine, the stimulating effect on propulsive motility exceeds that following the administration of 0.5 mg. of Prostigmine, and colonic transport is very active. Oral administration of 1 mg. of ergota-

mine with 15 mg. of Prostigmine also is followed by increased transport. Atkinson[52] believes that this combination of drugs is extremely useful in treating megacolon and similar disorders.

Posterior Pituitary Extracts

Much argument has been expended over the question whether pressor substances extracted from the posterior pituitary gland stimulate or inhibit intestinal motility. At present, there is a tendency to believe that the stimulating effect predominates in man and that the inhibitory effect is characteristic of the dog.[20, 47] That species difference is not the whole answer, however, is shown by the fact that some authors,[22, 53] have not observed a stimulating effect from posterior pituitary extracts in man (B and O), and others[54] have noted increased transport in the dog (X and O). Some contradiction may arise because the stimulating effect of these pressor substances on the intestinal musculature may, as Larson[55] suggests, be variably antagonized by vascular constriction and anoxia of the bowel. Furthermore, the reaction of the bowel to intravenous and subcutaneous doses varies considerably (B).[55]

If motility and transport are not confused, and if balloon-propulsion is not identified too strictly with flow of gas and chyme, it appears that some of the reports concerning the action of pituitary extracts are not so contradictory as they may seem. In man, the tone of the jejunum and ileum is lowered, but propulsive waves are increased in frequency by an intramuscular injection of 5 to 10 units (B).[32] The colon also exhibits an increased number of strong propulsive waves after 1 or 2 units has been given intramuscularly, but the increase in propulsive motility is accompanied by a decrease in total motility (B).[47] If mixing waves are unaffected, this can only mean that tone is depressed, a fact that is apparent in the kymographic record reproduced by Adler et al.[47] Hence, it appears that in man posterior pituitary extract lowers tone moderately but increases and co-ordinates propulsive waves, a state of motility that is favorable to transport. These considerations make it clear why this drug is used clinically to eliminate gas shadows (X)[56] or to relieve ileus,[57] even though motility as a whole may be decreased.

In the dog, 1 to 15 units of posterior pituitary extract inhibits motility, but the effect is less marked in the proximal colon (B),[47] where an actual stimulation of wave activity may occur (B).[58] Furthermore, it has been noted that wave activity is depressed less easily than is tone (B).[20, 55] These observations suggest that even though the drug has a strong inhibitory effect in the dog, it may establish intraenteric pressure gradients favorable to the transport of fluid and gas.

Pituitary extract acts quickly — within two to three minutes after injection — and its effect lasts for fifteen to twenty minutes. It is thus used with advantage when rapid action is desired, but in general, Prostigmine — a more reliable drug with less side effects — is preferred. When both drugs and ergotamine are combined in subcutaneous injection (Prostigmine 0.25 mg., ergotamine 0.25 mg. and pituitary extract 1.25 units), a rapidly acting, potent and long-lasting increase in transport can be obtained (B).[47]

Vitamins

Although vitamins are not strictly drugs, their use as therapeutic agents is so common today that a brief survey of their effect on intestinal motility seems warranted. A possible relation between vitamins and intestinal function is, of course, suggested by the fact that intestinal disorders are characteristic of many deficiency diseases. The ulcerative and inflammatory changes involving the intestinal mucosa of severe cases doubtless account for some of these disorders, but a somewhat more direct mechanism was proposed in 1919 by McCarrison,[59] who suggested that intestinal motility might be deranged in vitamin deficiencies principally because of degenerative changes in the myenteric plexuses. The basis for his suggestion was his observation that marked degeneration of Auerbach's plexus occurred in pigeons and guinea pigs kept on a diet deficient in vitamins A, B and C. Similar observations have recently been made in monkeys.[60]

The demonstration that vitamin deficiencies, particularly those of the vitamin B complex, can induce morbid changes in the structure of intestinal plexuses raised the possibility that the function of these nerve cells might also depend on an adequate supply of certain vitamins. The anorexia that is an early feature of deficiency of vitamin B complex[61] and the roentgenologic changes that appear in the small intestine during deficiency states[58, 61, 62] also suggest that function may be altered before structure is affected.

Intestinal strips removed from animals deficient in various fractions of vitamin B complex exhibit diminished motility when compared to the normal[63, 64, 65]; and thiamine, which has no effect on the normal excised intestinal muscle,[66, 67] can stimulate motility of strips taken from animals deficient in vitamin B_1.[66] If dogs are put on a black-tongue-producing diet, changes in intestinal motility, usually in the direction of a hypermotility, may occur before lesions of the tongue develop.[68] In an attempt to elucidate these effects of defi-

ciency of vitamin B complex, particularly thiamine deficiency, Antopol et al.[65] found that the serum and duodenal tissues of pigeons with beriberi have an increased cholinesterase content and are less sensitive to acetylcholine. These observations have led Glick[69] to suggest that thiamine acts as a physiologic conserver or potentiator of acetylcholine in the organism through its inhibiting effect on cholinesterase.

In spite of the evidence that has been obtained with respect to thiamine chloride, many authorities are aware that nonspecific changes may occur during deficiency states, and hesitate to claim that thiamine exerts a specific control over intestinal motility. Thus Cowgill,[70] in 1938, concluded that the lack of vitamin B_1 produces no specific dysfunction of the organs of the alimentary tract. The same may be said of other purified fractions of the vitamin B complex. Whereas it is interesting that the transport of a barium meal in the dog is accelerated if the meal contains inositol and decreased if it contains niacin (X),[71] caution must be exercised in accepting the conclusion that these vitamins are directly concerned with intestinal motility and that the ratio of niacin to inositol is the nutritional factor that determines hypomotility or hypermotility.

Present-day knowledge indicates that no vitamin or group of vitamins directly stimulates or inhibits intestinal motility. The lack of certain vitamins, particularly those of the vitamin B complex, does, however, alter motility, presumably by deranging the function and structure of the intestinal mucosa, musculature and nervous tissue.

65 East Newton Street

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**
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CASE 29281

PRESENTATION OF CASE

A sixty-four-year-old fisherman entered the hospital because of an "aching pain in the small of the back."

Five weeks before entry while pulling a dory onto the beach, he experienced rather sudden pain in the small of the back and under the left shoulder blade. A physician strapped his back, but this afforded little relief. The pain intermittently recurred, and about three weeks later the backache became gradually more severe and at times on exertion a sharp pain radiated from the back around to the left anterior costal margin. During the week prior to admission the pain became constant and seemed to be in the region of the eighth and ninth dorsal vertebras. During that time he lost his appetite and felt weak but had no specific gastrointestinal complaints, such as nausea, vomiting, gas, abdominal pain and jaundice. The patient had always been constipated but in the two weeks prior to admission he believed that the constipation was severer. At no time did he recognize bloody or tarry stools. During the previous two months he had lost 15 to 20 pounds.

The family history was noncontributory. For many years the patient had had a chronic cough occasionally productive of small amounts of brownish sputum. At no time was the sputum blood streaked, and repeated sputum examinations were said to have been negative for tubercle bacilli, though "roentgenographic studies showed some trouble in the lungs." Thirty years before entry he had had "bronchitis" and occasional night sweats.

Physical examination disclosed a thin, apprehensive man who complained bitterly of acute, constant, low-back pain. The examination of the heart was normal. There was a 3-cm. firm, exquisitely tender mass at the angle of the left tenth rib. There was dullness with increased voice sounds and bronchovesicular breath sounds at the right apex anteriorly and at both lung bases; fine moist rales were audible at both lung bases posteriorly. The abdomen was difficult to examine because it was held tense, apparently as a result of the patient's fear of further discomfort. No masses were felt and no tenderness could be elicited. The abdomen was tympanitic, and normal peristalsis was present. There was slight limitation to forward bending of the neck, without pain or a positive Kernig's sign. There was exquisite tenderness over the spinous processes of the tenth to twelfth dorsal vertebras, with some tenderness of the posterior portions of the tenth, eleventh and twelfth ribs; however, no muscle spasm could be detected. The extended legs were easily flexed on the trunk without pain. The arms and legs were normal except for varicose veins of the legs, more marked on the right. Several examiners felt a superficial, movable lymph node in the left supraclavicular region. The prostate was small and rather hard, but was not tender. No rectal masses were felt. A neurologic examination demonstrated reflexes within normal limits. Vibration sense was diminished at the ankles, more so on the left. Sensation was normal except for hyperesthesia, particularly on pressure upon the twelfth dorsal spinous process and the right tenth rib in the midclavicular line. There was marked longitudinal ridging of the nails.

The blood pressure was 124 systolic, 88 diastolic. The temperature was 98°F., the pulse 80, and the respirations 20.

Examination of the blood revealed a red-cell count of 3,830,000, with a hemoglobin of 70 per cent, and a white-cell count of 18,420, with 86 per cent neutrophils, 10 per cent lymphocytes and 4 per cent monocytes. Twenty-four hours later the white-cell count was 20,400. The urine was normal. A blood Hinton test was negative. A tuberculin (1:50,000 dilution) test was negative. Examination of the sputum and gastric contents was negative for acid-fast organisms. The clotting time was 4 minutes; the bleeding time, 19 minutes. The stools were guaiac positive on two occasions and negative on three subsequent examinations. The nonprotein nitrogen was 28 mg. per 100 cc., the chloride 102.1 milliequiv. per liter, the van den Bergh 0.85 mg. direct and 1.2 mg. indirect, the protein 4.9 gm. per 100 cc., the albumin being 2.3 gm. and the globulin 2.6 gm.—an albumin globulin ratio of 0.88. The calcium was 10.0 mg., the phosphorus 4.6 mg. and the phosphatase 17.6 Bodansky units per 100 cc. A lumbar puncture revealed an initial pressure of 75 mm. of water; the dynamics were normal. The spinal-fluid protein was 51 mg. per 100 cc.; the fluid did not contain cells. The gold-sol curve was normal.

*On leave of absence.

An x-ray film of the lower dorsal spine demonstrated marked degenerative changes — spurring and lipping — consistent with hypertrophic arthritis; there was no definite evidence of metastases. The rectum and cecum filled without delay during a barium enema. No evidence of disease of the rectum and large bowel could be demonstrated. A chest roentgenogram revealed that the diaphragm was low in position, and fluoroscopy showed impaired respiratory motion. The lung fields were large and bright and were not involved by disease. The precordial space was large. Both upper lung fields contained string-like areas of increased density with some flecky areas, particularly on the left side. The left hilus was elevated. There was a circumscribed area of consolidation in the anterolateral portion of the left lower lobe close to the diaphragm. The pleura showed evidence of thickening in this region. Far posteriorly on the left side, superimposed on the shadows of the fifth and sixth dorsal vertebras, was a soft-tissue mass with a sharply defined convexed anterior border that blended smoothly with the pleura. It was not visible in the anteroposterior view. The seventh and eighth dorsal vertebras were slightly wedged, but they showed no evidence of bone destruction. Following a barium meal, examination of the upper gastrointestinal tract showed a normal esophagus. The stomach appeared large, atonic and moderately dilated and contained a large amount of fluid. Barium passed readily through the somewhat widened first, second and third portions of the duodenum with a to-and-fro motion in the second and third portions. Fluoroscopically the duodenum was slightly narrowed near the ligament of Treitz and barium passed through the area in splashes; no actual obstruction was present, and no evidence of intrinsic or extrinsic disease could be demonstrated on the films.

On the eighth day after admission the patient seemed more comfortable, although he had only been treated symptomatically. The swelling over the tenth rib had decreased in size. On the following day, however, he was markedly dyspneic. The back pain, however, had disappeared. The temperature was 101°F. The scleras were slightly icteric, and the skin had a slight lemon tint. Dyspnea was severe, but the lungs were clear except for crackling rales at the left base. The heart could not be satisfactorily outlined because of moderate emphysema. The neck veins were distended and pulsating but the wrist pulse was regular. The blood pressure was 120 systolic, 50 diastolic. The abdomen was tense and tympanitic. Examination of the blood revealed a red-cell count of 1,040,000, with a hemoglobin of 6.3 gm., and a white-cell count of 35,000, with 54 neutrophils, 5 per cent metamyelocytes, 9 per cent myelocytes, 16 per cent questionable blast forms, 13 per cent lymphocytes, 2 per cent monocytes and 1 per cent basophils. The platelets were markedly depressed, and there was marked anisocytosis, poikilocytosis and polychromatophilia of the red cells. The blood picture remained essentially the same for the next few days. He gradually became extremely disoriented and died twelve days after admission.

Differential Diagnosis

Dr. Rulon W. Rawson: To summarize, we have a sixty-four-year-old fisherman complaining of an increasingly severe backache, anorexia, weakness and loss of weight. The significant physical findings were tenderness over the lower dorsal spinous processes and over the posterior portion of the lower ribs, a palpable supraclavicular lymph node and terminal jaundice. The significant laboratory findings included a moderate hypochromic anemia that changed to a marked hyperchromic anemia associated with an impressive myelogenous leukemoid picture, a low blood protein and an elevated blood phosphatase. X-ray examination revealed unusual shadows in the left lung field, nothing definite in the gastrointestinal tract and no evidence of spinal metastasis, although the seventh and eighth dorsal vertebras were wedged.

The finding of a supraclavicular node, two masses in the chest cavity, pain in the back, a myelophthisic anemia and an increased blood phosphatase suggest a widespread neoplastic process with metastases to the lymph nodes, spine, ribs and bone marrow and a primary or secondary carcinoma in the chest. The low total protein points to liver disease, as does the late finding of jaundice. The increased blood phosphatase might have been due to liver metastases, as well as to an osteoblastic reaction around a metastatic lesion in the skeleton. The dilated stomach and duodenum, with the described to-and-fro movements in the distal part of the duodenum, indicate some obstruction distal to the lower third of the duodenum. Primary tumors of the small bowel are so rare that I shall not consider such a diagnosis and shall explain the apparent obstruction on the basis of pressure from retroperitoneal lymph nodes containing metastatic cancer.

The slightly increased spinal-fluid protein with the rather low initial pressure might indicate a partial block due to spread of disease from the involved vertebras to the spinal canal.

The most obvious diagnosis to make is that of bronchiogenic carcinoma with generalized metastases. Carcinoma of the prostate with metastasis

might give a picture similar to the one presented by this patient. However, with carcinoma of the prostate it is commoner to see definite x-ray evidence of disease involving the pelvis and spine and less common to see metastases to the liver, lungs and retroperitoneal nodes. Lymphoma might also produce this picture. At this man's age the Hodgkin's or reticulum-cell sarcoma types would be the ones to consider. However, the spleen was not described as palpable and only one peripheral lymph node was felt. It is my impression that jaundice is a rare finding in lymphomatous disease. The blood picture is suggestive of a myelogenous leukemia, but I prefer to interpret it as indicative of a myelophthisic anemia due to bone-marrow metastases. My diagnosis is bronchiogenic carcinoma with metastases to the pleura, vertebras, ribs and liver and to the mediastinal, retroperitoneal and left supraclavicular lymph nodes.

Dr. George W. Holmes: I find it a rather complicated job for me to interpret even what is said in the text here. I shall try to point out as many of the things as I can. First, I think we can rule out the gastrointestinal tract as a source of trouble. There is nothing in the text that points to disease, and certainly I am not able to see anything in the films.

So far as the spine is concerned, it is obvious that there are spur-like formations, which are not uncommon in people past middle life. I should not expect that to cause any trouble except vague back pain. I do not believe that the "wedge-shaped vertebras" are of great clinical significance in an old person with marked curving of the spine. If each were accompanied by a widening of the body and a destructive process in the bone, one would have to pay attention to them. I do not see anything of that kind, however, and I am inclined to put little weight on that part of the findings. The anterior margin of the tenth or eleventh dorsal vertebra shows a concave defect. It is not very clear on this film, which is the only one we have. I shall have to leave the spine without giving any help.

The chest shows an obvious lesion. The hilus was said to be high on the left side, which is obvious. That usually means either fibrosis in the lung or a partial collapse of a lobe — something contracting the upper part of the chest. The films also show a good deal of change in the substance of the lung in the upper part of the chest, probably the upper lobe, and at the base there is obliteration of the costophrenic sinus. On the right side I think the diaphragm is normal. The low position may not mean anything or may mean the patient had a moderate degree of emphysema. According to the fluoroscopic examination there was no marked limitation of the movements of the diaphragm, which one would expect with emphysema.

Clinical Diagnoses

Metastatic malignancy, primary site undetermined.
Myelophthisic anemia.

Dr. Rawson's Diagnoses

Bronchiogenic carcinoma, with metastases to vertebras, ribs, liver, pleura and mediastinal, left supraclavicular and retroperitoneal lymph nodes.
Myelophthisic anemia.

Anatomical Diagnoses

Adenocarcinoma of stomach, with metastases to pleura, lung, vertebras, ribs and mediastinal, left supraclavicular and retroperitoneal lymph nodes.
Myelophthisic anemia.
Hematopoiesis of spleen and liver.
Neoplastic thrombosis of small pulmonary arteries.
Pulmonary tuberculosis, healed.
Pulmonary infarct.

Pathological Discussion

Dr. Benjamin Castleman: As Dr. Rawson predicted, this man had a myelophthisic anemia. The vertebral and femoral marrow was almost completely replaced by metastatic carcinoma. In these cases the spleen and, if the marrow replacement is widespread, the liver take on the function of manufacturing red cells, and such was the case here. Both the liver and spleen had foci of hematopoiesis. The primary site of the cancer was not in the lung, but in the cardia of the stomach, 1 cm. below the cardiac orifice on the lesser curvature. I suppose that if the patient could have been stood on his head during the x-ray examination it could have been seen. The two positive guaiac tests on the stools furnished the only lead.

A Physician: How do you account for a decrease of over 2,000,000 in the red-cell count during his short hospital stay?

Dr. Castleman: A tremendous loss of red cells in nine days certainly suggests hemorrhage, but there was no evidence of it in the gastrointestinal tract or anywhere else.

A Physician: Why did he have a white-cell count of 35,000?

Dr. Castleman: That is unusual, but it may be moderately elevated in myelophthisic anemia.

I am quite sure he had nucleated red cells in the smear, which were not recorded. But nucleated red cells are rarely noted in any hematologic examination so I always assume they are there when I want to have them. One other finding was quite interesting and may have had something to do with the distended pulsating veins in the neck: the patient had no pulmonary emboli, but every small artery in the lung was filled either with tumor thrombus or with secondary fibrous thrombosis, so that he had, in the terminal stages, an acute cor pulmonale. A similar case was described several years ago by Brill and Robertson.* In their case also, the primary carcinoma was in the stomach.

DR. RICHARD CHUTE: Was the back pain due to pathologic fracture?

DR. CASTLEMAN: We did not find any major destructive lesion in the vertebra, although there was diffuse tumor destruction in the marrow. When I read the story through I thought of cancer of the pancreas because I have seen a number of cases of cancer of the tail of the pancreas in which the patients had attended the Orthopedic Clinic anywhere from six months to two years, getting one back brace after another until finally the tumor mass was apparent. This man had a number of enlarged lymph nodes about the celiac axis in immediate apposition with the pancreas but not involving it. I am inclined to think that there was direct nerve invasion at that point, which was the source of the pain. That is a guess however.

DR. HOLMES: Is there any reason why the lung hili were high?

DR. CASTLEMAN: Yes; the patient had old fibrotic processes at both bases, which I think quite certainly were due to healed tuberculosis. He also had an area of fibrosis at the left base that looked like a healed infarct of many years' standing.

DR. HOLMES: We have recognized for some time that widespread cancer in the bone marrow can exist without changes in the bone by x-ray. I perhaps should have mentioned that in discussing the case.

DR. CASTLEMAN: There were no liver metastases. The soft-tissue shadow seen on the x-ray film close to the dorsal vertebras was a metastasis to the sixth rib, which formed an elliptical soft-tissue mass near the costovertebral junction. Similar but smaller metastases involved the ninth and tenth ribs on the left side.

*Brill, I. C., and Robertson, T. D. Subacute cor pulmonale. *Arch. Int. Med.* 60:1043-1057, 1937.

CASE 29282

PRESENTATION OF CASE

A sixty-five-year-old man, a woolworker, entered the hospital because of jaundice and itching of the skin.

He was well until four months prior to admission when he noticed the onset of itching of the skin. He considered this a "yarn itch" since many other workers had had the same trouble and "scratched the hide off themselves." Three and a half months before entry he experienced on two occasions, a week apart, a sudden, cramping, diffuse, lower abdominal pain, which lasted only a few minutes and was not severe enough to double him up or force him to stop working. There was no nausea, vomiting, fever or chills. At about that time he developed a dislike for fatty foods and noticed that his urine had become much darker in color and his stools clay colored, but there was no change in bowel habits. Two and a half months before entry he developed anorexia and felt so tired that he had to give up work. His physician told him that the itch was not "yarn itch" and gave him a lotion; he went to work in a shipyard. Two months before admission his fellow workers noticed that he was jaundiced. The jaundice gradually deepened, and six weeks prior to admission his physician treated him with pills, which were said to have reduced the jaundice somewhat. He denied the use of alcohol or drugs.

There was no family history of jaundice. His mother died of carcinoma of the bowel. The past history was noncontributory.

Physical examination disclosed a fairly well-nourished man who was moderately jaundiced. The scleras were deeply jaundiced. The lungs were normal. A soft systolic murmur was audible at the apex of the heart. The abdomen was soft but there was slight resistance to deep palpation in the right upper quadrant. A smooth, hard liver edge was palpable two fingerbreadths below the costal margin.

The blood pressure was 145 systolic, 75 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood revealed a red-cell count of 3,500,000, with a hemoglobin of 12.5 gm. per 100 cc. and a white-cell count of 10,900, with 73 per cent neutrophils. The urine gave a + test for albumin and +++ test for bile; the sediment was negative. A blood Hinton test was negative. The stools were clay colored, soft, formed and repeatedly guaiac negative. The protein was 7.2 gm., the albumin 4.8 gm. and the globulin 2.4 gm.

per 100 cc. The van den Bergh was 6.8 mg. direct, and 9.8 mg. indirect. The prothrombin time was 32 seconds (normal, 22 seconds), the carbon dioxide combining power 15.3 millimols per liter, the chloride 97.0 milliequiv. per liter, the phosphorus 3.7 mg. per 100 cc., and the phosphatase 15.8 units per 100 cc. A cephalin flocculation test was 0 at 24 and 48°C.

A gastrointestinal series disclosed a normal esophagus, stomach and duodenum. No evidence of encroachment on the stomach or duodenal loop by an extrinsic tumor was observed, and there was no infiltration of the duodenum. A film of the right upper quadrant showed no evidence of gallstones. Chest x-rays were negative.

On the sixth day the patient began to run a spiking temperature, ranging from 100 to 103°F. This continued for six days and then subsided completely. The white-cell count varied from 8000 to 12,000. An occasional stool was light brown but most of them were clay colored. On the tenth day duodenal drainage yielded amber fluid containing a few white cells and calcium bilirubin crystals. He continued to be deeply jaundiced.

After preoperative preparation, including saline glucose infusions and water-soluble vitamin K, an operation was performed on the nineteenth hospital day.

Differential Diagnosis

Dr. Edward Hamlin, Jr.: The first question to decide is whether or not we are dealing with true obstruction or intrahepatic jaundice. The evidence, particularly the laboratory findings and the description of the liver on palpation, is strongly suggestive of obstructive jaundice. Is the obstruction on the basis of tumor or of stone? In favor of the former is the age of the patient and the history of gradual painless onset. Incidentally, the severe itching might be interpreted in favor of obstructive as opposed to intrahepatic jaundice.

The two episodes of lower abdominal crampy pain, although they might be attributed to biliary colic, are so atypical that it is unwise to consider them as such. The laboratory findings enable one to say only that the patient was moderately jaundiced, had a mild anemia of the secondary type and had no evidence of liver damage as evidenced by globulin tests, both as regards amount and qualitatively (cephalin flocculation test). One would like to know whether the low carbon dioxide combining power was a reflection of abnormal carbohydrate metabolism.

The x-ray examination does not help at all, although occasionally a careful study of the duodenum is of great assistance in such cases.

One must attribute the six days of spiking temperature to cholangitis or to infection entirely unrelated to the primary disease. As Dr. Arthur W. Allen has often pointed out, an occasional brown stool in a series of completely clay-colored ones is commoner in association with carcinoma in the region of the ampulla than with stone, a fact that is presumably attributable to necrosis and sloughing of the tumor, which allow some bile to escape.

Thus far the evidence has tended to point strongly toward the diagnosis of tumor in the region of the head of the pancreas or of the extrahepatic biliary tract. But someone ordered a duodenal drainage, and the report came back that calcium bilirubin crystals were present. If the observation was made by an experienced man, that single fact outweighs in my mind all the piled-up evidence in favor of tumor. Of course it is conceivable that the patient may have had both stones and tumor; but if one diagnosis is to be made, the presence of calcium bilirubin crystals in the duodenal drainage causes me to make the diagnosis of common-duct stone a heavy favorite.

Dr. Clifford C. Franseen: We approached the problem much as Dr. Hamlin did, believing that a tumor in the region of the head of the pancreas could not be excluded. At operation the liver appeared to have undergone moderate cirrhotic changes. The gall bladder was found to be distended and free of stones. The common duct was dilated to between 2.0 and 2.5 cm. in diameter. There was a fairly discrete mass in the head of the pancreas, contiguous to the wall of the duodenum, which felt to be about 3 cm. in diameter. Its consistence was characteristic of carcinoma. Because of the patient's long-standing jaundice, it was thought that a two-stage procedure should be done. Accordingly a cholecystojejunostomy was performed as the first stage.

Fifteen days later the second stage was carried out. The pylorus, the first and second portions of the duodenum, the distal half of the common bile duct and the head of the pancreas were resected en bloc. It had been hoped that the end of the third portion of the duodenum could be sutured over the cut end of the pancreas, but this proved to be mechanically impossible, and attempts to fit a loop of jejunum against the cut end of the pancreas produced such a sharp angulation of the bowel that its function would undoubtedly have been too greatly jeopardized. This was due to the fact that the cut end of the pancreas lay in an extraordinarily deep hole. Exteriorization of the cut end of the pancreas was therefore resorted to by drainage anteriorly. This seemed the most direct route, especially since drainage through the

right flank would have had to pass beneath the cholecystojejunostomy. A posterior Polya gastrojejunostomy was done.

Clinical Diagnosis

Common duct stone?
Tumor of head of pancreas?

Dr. Hamlin's Diagnosis

Common duct stone?
Carcinoma of ampulla?

Anatomical Diagnosis

Adenocarcinoma of common bile duct.

Pathological Discussion

Dr. Benjamin Castleman: The specimen received in the laboratory consisted of the distal portion of the stomach, about 10 cm. of duodenum and the head of the pancreas with the distal 5 cm. of the common bile duct coursing through it. The proximal half of the bile duct was dilated, measuring 2.5 cm. in circumference, but the distal half was narrowed to a circumference of 0.7 cm. There the mucosa was roughened and covered with grayish-white granular tissue, which histologically proved to be adenocarcinoma. The tumor invaded the wall of the bile duct and also blocked the opening of the pancreatic duct, which opened into the bile duct just above the sphincter of Oddi. The pancreatic duct was slightly dilated.

Dr. Hamlin placed a good deal of weight on the presence of calcium bilirubin crystals in the duodenal drainage specimen. How valuable is this test, Dr. Jones?

Dr. Chester M. Jones: The diagnostic value of a study of duodenal contents in these cases has been proved by many years' experience. Like every other laboratory test, however, it is subject to exceptions, and therefore must be interpreted in relation to the clinical picture. If a good specimen of duodenal contents is obtained and it is found that the sediment contains moderate or excessive amounts of calcium bilirubin and cholesterol crystals, then the diagnosis of biliary calculi is reasonably certain. If a fair number or an excessive number of cholesterol crystals are obtained, then the same diagnosis should be reasonably considered. Where, as in this case, the sediment contains only white cells and calcium bilirubin crystals, then a more detailed examination should be made of the duodenal contents for other elements, and it should be correlated with the clinical picture. Prolonged biliary stasis, such as may occur in infectious hepatitis or in a prolonged period of extrahepatic obstruction, may cause a precipitation of calcium bilirubin crystals and the appearance of small masses resembling casts. When a flow of bile is re-established, these elements are found for a few days, the casts consisting of mucus, detritus and bile-stained material. Not infrequently, particularly in infectious hepatitis, groups of bile-stained white cells are also noted. Under circumstances such as this patient experienced, with prolonged jaundice and a subsequent flow of bile, which must have been obtained when a duodenal drainage was performed, the appearance of some calcium bilirubin crystals and some white cells in the stasis bile is not diagnostic, and too much stress must not be laid on it.

Dr. Franseen: The patient did well postoperatively until the fourth day, when bilateral ligation of the superficial femoral veins for deep thrombophlebitis had to be done. Drainage of pancreatic juice from the sinus tract was profuse. On the thirteenth day the patient had a small hemorrhage from the tract and on the thirty-first day a second hemorrhage. He died a few hours later.

Dr. Castleman: The postmortem showed that the space previously occupied by the resected head of the pancreas and duodenum was replaced by an abscess cavity filled with purplish necrotic material that had eroded into the sutured end of the common bile duct and also into the main portal vein. The result was the development of a pylephlebitis, with numerous abscesses of the liver.

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The Journal does not hold itself responsible for statements made by any contributor.

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STARVING EUROPE

The January 9, 1943, issue of the *British Medical Journal* brings forcibly to one's attention the herculean task of relief in Europe that will face the Allied Nations after the war. Most urgent, of course, will be the provision of food and shelter for the millions still living but rendered destitute and starving by the paternal ministrations of the "master race." After this will come medical care of the sick, social reorganization and, as soon as possible, re-establishment of agriculture and industry.

Efforts are, even now, constantly being made to render what aid is possible to the starving inhabitants of the conquered nations, but the amount that can be sent and the uncertainty of its getting by so ruthless an enemy render the total results pitifully inadequate. The British Famine Relief Committee has estimated the quantities of dried milk and vitamins needed to save the children of Greece and Belgium, and Sweden has expressed its willingness to carry on this relief. Under the present arrangement 100 tons of powdered milk, in addition to the monthly supply under navicerts of 15,000 tons of wheat, will be and has been dispatched to Greece in Swedish vessels, to be distributed by the International Red Cross.

The need, however, is appalling. In Athens, 100,000 out of 1,000,000 have died of starvation and disease. As early as December, 1941, according to the Athens Welfare Center, 9 out of 10 babies were dying in their first six months because of starvation of their mothers and the lack of milk, practically all the cattle having been slaughtered. From eye-witness accounts: "The children had not even the strength to beg, and some had died as they crouched over a grating; they seemed to be asleep, and hours might pass before their companions realized they were dead. . . . Orphans and abandoned children are found wandering in the streets . . . starving, dirty, pale and thin. . . . They stop at nothing to find a bit to eat, searching among refuse and fighting the dogs for something edible." In June, 1942, in one temporary hospital in Athens, four children were found to a bed. In Belgium, the infant mortality has quadrupled since 1939, with the tuberculosis morbidity increased from 30 to 80 per cent. Thus has the world benefited from that famed *Kultur* of which our adversaries are so proud!

The combined medical and nursing resources of the Allied Nations must also be mobilized, for the apocalyptic horsemen still ride together, and pestilence follows famine as surely as famine follows war. Not only is tuberculosis on the increase but malaria, typhus and the enteric diseases will have to be combated, and scientific nutritional measures put into effect.

The state of so much of the world renders it increasingly imperative that this war be won by the nations that are opposing the slave system of society. After the war, all alliances must be assiduously preserved, for a new world will have to be constructed on the ruins of the old. Friendships must be cultivated, and resources must be husbanded, for there will be desperate need of them both.

A SEMICENTENNIAL OF OSLER'S *PRINCIPLES AND PRACTICE OF MEDICINE*

Fifty years ago last year, in 1892, there was published by the D. Appleton and Company of New York, William Osler's *Principles and Practice of Medicine*, intended for the use of practitioners and students of medicine. The appearance of the fourteenth edition in 1942, rewritten in large part by Henry A. Christian but still based on the sturdy design and structure established by Osler, marks the vigor and soundness of this book, one of the great contributions to medical literature. As Cushing pointed out in his *Life of Osler*, the work began seven or eight years before the actual publishing of the first edition. Osler, during those years, wrote various editorials for the *Medical News*, of Philadelphia, and thus kept himself in touch with the new and important ideas in medicine, and when he composed his medical masterpiece, he did it with a thoroughness and a sureness of touch that were immediately apparent to all his contemporaries. In addition, he wrote in such a readable form that this book immediately superseded all other textbooks of general medicine, and has continued to hold a place in the field for fifty years. It was based on sound pathology plus a wide knowledge of clinical medicine. Its sale was so rapid that the first printing, three thousand copies, was sold out in two months, an unprecedented sale for a book of this type. A few corrections were made in the second printing of the first edition. Subsequently, there have been issued nineteen editions in English (thirteen published in America and six in England), three and an appendix in Chinese, and one each in French, German and Spanish.

In the Boston Medical Library a section is devoted to the editions of this book, where there are examples of all the editions with many variants, numbering over ninety. The history of this book should some day be written for in it, if successive editions are examined, will be found the history of the advancements in clinical medicine in the last fifty years. The last edition, rewritten by Dr. Christian, is a worthy successor to a long line of previously published volumes. In honor of this semicentennial volume, the *Journal* extends congratulations to both Dr. Christian and the D. Appleton–Century Company.

MEDICAL EPONYM

Wilson's Disease

The essay "Progressive Lenticular Degeneration: A familial nervous disease associated with cirrhosis of the liver" formed part of a thesis by S. A. K. Wilson (1878–1936). The monograph appeared in *Brain* (**34:** 295–509, 1912), and the following is a quotation from pages 486 and 487:

> Progressive lenticular degeneration is a disease of the motor nervous system, occurring in young people and very often familial. It is not congenital or hereditary.
>
> It is progressive and fatal within a varying period; acute cases may last only a few months . . . the average duration of chronic cases is four years.
>
> It is characterized by a definite symptom-complex, whose chief features are: generalized tremor, dysarthria and dysphagia, muscular rigidity and hypertonicity, emaciation, spasmodic contractions, contractures, emotionalism. . . .
>
> Although cirrhosis of the liver is constantly found . . . there are no signs of liver disease during life. . . .
>
> The chief pathological feature of the disease is bilateral symmetrical degeneration of the putamen and globus pallidus, in particular the former. . . .
>
> A constant, essential and, in all probability, primary feature of the pathology of the disease is cirrhosis of the liver, not syphilitic or alcoholic.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

ABBE — Elizabeth M. Abbe, M.D., of Roxbury, died January 18. She was in her sixty-ninth year.

Dr. Abbe received her degree from Tufts College Medical School in 1909. She was a member of the Massachusetts Medical Society and the American Medical Association.

FRANK — MORRIS FRANK, M.D., of Roxbury, died June 17. He was in his fifty-seventh year.

He received his degree from Harvard Medical School in 1911. He was a councilor of the Massachusetts Medical Society, a member of the American Medical Association and the American Association of School Physicians. He was a staff member of the Beth Israel Hospital, the Jewish Memorial Hospital and the Washingtonian Hospital.

His widow and a son survive.

MERCHANT — RAYMOND F. MERCHANT, M.D., of Vineyard Haven, died June 7. He was in his forty-second year.

Dr. Merchant received his degree from Middlesex University College of Medicine. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow survives.

PHILLIPS — MAJOR ROBERT T. PHILLIPS, former Boston physician, died in a Japanese prison camp in the Philippines. He was in his forty-second year.

Dr. Phillips graduated from Bowdoin College in 1924 and Tufts College Medical School in 1932, and afterward served on the staff of the Boston City Hospital. He was called into active service from the Medical Reserve Corps several months before the attack on Pearl Harbor and was at Manila when war was declared; following the evacuation of Manila he presumably went to Bataan. Dr. Phillips was a member of the Massachusetts Medical Society and the American Medical Association.

His widow and four children survive, as well as his twin brother, Dr. Richard B. Phillips.

WRIGHT — ALLEN H. WRIGHT, M.D., of East Northfield, died June 17. He was in his sixty-sixth year.

Dr. Wright received his degree from the University of Maryland School of Medicine and College of Physicians and Surgeons in 1906. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow and two daughters survive.

MISCELLANY

BREAKDOWN IN EARLY TUBERCULOSIS

Too often we substitute words for action. We repeat the same soul-satisfying phrases until we endow them with a magic and totally undeserved quality of being able to accomplish miracles. Miracles do not just happen. What look like miracles generally turn out to be the result of careful planning, devotion to sound principles and an unlimited amount of tenacity and hard work. The "early discovery" of pulmonary tuberculosis, by which is meant discovery of the disease in a minimal stage, is an empty accomplishment unless it can be followed by thorough treatment without delay. The following abstract of a recent paper (Stein, S. C. Breakdown in early tuberculosis. *Pub. Health Nursing* **35**:140–142, 1943) is pertinent.

* * *

The prevalent opinion that the finding of active tuberculosis in a minimal stage warrants an excellent prognosis is true only when adequate treatment follows at once. Many of the favorable reports have come from sanatoriums, where the outlook on minimal pulmonary tuberculosis is not the same as that in the clinics at the time of the early diagnosis.

In sanatoriums the number of minimal cases has not increased in direct proportion to the number of cases found on the outside. Failure to see and follow many diagnosed cases may explain this impression. Some patients who reach the sanatorium with minimal disease may show no unfavorable progression even though weeks or months elapsed between the time of discovery and the beginning of institutional care. These are the more resistant cases. Conversely, a significant number of patients found in surveys, and particularly among those in contact with sputum-positive tuberculosis, demonstrate low resistance and a rapid progression of their disease before sanatorium care is finally sought and obtained.

In the Henry Phipps Clinic, Philadelphia, Pennsylvania, even though the serious potentialities of minimal pulmonary tuberculosis are recognized and the physicians and nurses endeavor earnestly and persistently to overcome obstacles that prevent adequate care of these patients, results are astonishingly poor. A study of patients with minimal lesions has revealed that almost half developed progressive disease — true of both white and colored patients. Mortality figures were 25 per cent for the colored and 6 per cent for the white patients. Only one of the cases that died had obtained sanatorium care, and then only when the disease had progressed to an advanced stage.

What causes the poor results? The dominant factors will, largely, be applicable to most localities.

First, the diagnosis. It is universally accepted that the x-ray is the most efficient method. Visualizing the minimal lesion is not difficult, but evaluation of its status is not so simple or foolproof. There are three categories: lesions whose appearance indicates active, unstable disease, lesions considered of doubtful significance and lesions whose x-ray appearance suggests that complete healing has occurred.

Determination of the character of a lesion is based to a large extent on experience with previous similar lesions observed over long periods. Interpreting the objective film is a distinctly subjective procedure, and is of prime importance since it influences recommendations for treatment. Many chest experts advocate the follow-up of contact cases for a period of at least two years after known exposure ceases. It is obviously as necessary to follow for a similar period those cases in the second and third categories mentioned to ensure their diagnosis of stability.

Of the nearly 50 per cent of the institute's minimal cases that showed progression of the disease, 86 per cent developed extension within the first year, the remainder within three years. Serial x-ray studies enable the clinician to determine at the earliest time those cases in which the original estimate of the lesion's stability was faulty.

Following the diagnosis, a strong rapport between physician, nurse and patient is essential. The psychologic reactions of the patient to his disease and its treatment depend on the confidence he has in his medical advisers. It is difficult to convince a symptomless patient, often one who was found by survey means and not by his own seeking, to accept such "drastic" treatment as absolute bed rest. He often scoffs at the diagnosis, claims to feel well and refuses to co-operate.

People in contact with sputum-positive tuberculosis may submit to examination merely for the comfort of being told they are free of the disease. When their hopes are

dashed and they are confronted with their own unsuspected trouble, they may turn antagonistic and refuse to accept advice.

Again, society has done little to solve the problem of the family head who must leave behind a situation of destitution for the ones he loves by accepting treatment that must necessarily be a prolonged hospitalization.

Assuming that all these deterrents to treatment have been removed, the actual obtaining of hospital care is in many communities still a great problem, growing greater owing to wartime shortages of materials and personnel. Institutions that require positive sputum before admitting a patient are inviting dangerous progression before making available the badly needed bed. The tendency to regard minimal cases lightly and to treat them insufficiently is far too prevalent and often leads to inexcusable relapses. Reliance on the standards of twenty years ago, which call for dependence on physical signs, to determine the stability of lesions defeats the whole purpose of early-diagnosis surveys, since the case without clinical manifestations will receive neglect instead of the treatment and close supervision it deserves.

Early diagnosis is meaningless unless it leads at once to intelligent handling, prompt care and adequate follow-up, with eventual recovery and maximum rehabilitation the goal. — Reprinted from *Tuberculosis Abstracts* (July, 1943).

CORRESPONDENCE

DEPRIVATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held June 28, the Board voted to revoke the license of Dr. Philip L. Manfredi, 903 Beacon Street, Boston, because of gross misconduct in the practice of his profession.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOK REVIEWS

A Textbook of Gynecology. By Arthur H. Curtis, M.D. Fourth edition. 8°, cloth, 723 pp., with 401 illustrations. Philadelphia and London: W. B. Saunders Company, 1942. $8.00.

The fourth edition of Curtis's textbook is a thorough revision of an already excellent book. Not only has the subject matter been brought up to date, but many improvements and additions have been made.

The first 78 pages are devoted to the anatomy of the female pelvis and perineum. This section is a masterpiece and covers the subject thoroughly. The descriptions are clear, and there are many superb illustrations by Tom Jones.

On this foundation the author proceeds to cover the entire field of gynecology in a competent, complete and yet concise manner. Dr. Curtis is a genius at the difficult art of clear and succinct writing. There is no unnecessary verbiage to confuse and weary the reader. Not only medical students but practitioners will find this book an excellent review of the field, and even specialists will enjoy its lucid expositions.

The section on endocrine is rational and intelligent. Proper emphasis is placed on the sulfa drugs in the treatment of gonorrhea and other infections. Conservative treatment is stressed.

The discussion of tumors is extremely well done. Of special note is the statement that "radium treatment is more radical in its effects than surgical removal." Dr. Curtis quotes Robert Meyer as saying that it is impossible to classify ovarian tumors, and then classifies them. Like all such classifications, it leaves something to be desired. Furthermore, the relative frequency of the various types of tumors might well have been emphasized. Dr. Curtis seems a little too conservative in frowning on resection of the ovary. The reviewer believes that the operation is of value in certain cases. Moreover, a waiting policy, when confronted with a sizable ovarian tumor, may diminish the chance of recovery in malignancy, since operation before spread of the malignancy is as important with ovarian neoplasms as it is elsewhere. Preoperative differentiation is difficult, and if doubt exists, the reviewer is of the opinion that the patient should be given the benefit of that doubt.

The author's discussion of displacements and relaxation is excellent. It is based on his own work and shows the touch of the master. From the detailed instructions concerning the proper method of inserting a pessary to the descriptions of operative technics, this section is a model of medical writing.

There is no mention of vein ligation in the discussion of femoral thrombosis and pulmonary embolism. The treatment of "milk leg" by injection of the lumbar sympathetic nerves is also ignored. Since these constitute important advances in the treatment of not too rare complications of gynecologic surgery, they should certainly be mentioned.

Throughout the book Dr. Curtis's approach is sane, sound and conservative. As Lincoln might have said, "Anyone who wants a textbook on gynecology will find this a good book."

The Anatomy of the Nervous System from the Standpoint of Development and Function. By Stephen W. Ranson, M.D., Ph.D. Seventh edition. 4°, cloth, 520 pp., with 408 illustrations. Philadelphia and London: W. B. Saunders Company, 1943. $6.50.

The death of the author of this book was a great loss to neurology and America. He had established himself as a leader in the field of anatomy of the nervous system, as well as in neurologic research. Fortunately, the seventh edition was completed before Dr. Ranson's death, and the book is in the form that he would have desired to see it.

This text has become a standard work on the subject, gradually expanding through its numerous editions since 1920. The subject is presented in a dynamic manner, with emphasis laid on the developmental and functional significance of structure. In this edition certain chapters have been rewritten, particularly those on the sympathetic nervous system. The book has been slightly lengthened, and each page was carefully gone over by the author and his colleagues. Many suggestions from neuroanatomists have been incorporated into this edition, and the section on physiology has been considerably expanded. The volume, therefore, replaces previous editions as a text of outstanding value.

(Notices on page xii)

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NOTICES

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

The usual mid-summer meeting of the Middlesex South District Medical Society will not be held. This conclusion was arrived at by the officers after unsuccessful attempts were made to obtain a suitable meeting place. Gasoline rationing and more particularly, food rationing, have offered obstacles in making arrangements for the outing type of meeting.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 22

THURSDAY, JULY 22

*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, JULY 26

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, JULY 27

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

2:00–4:00 p.m. Myasthenia gravis clinic. Out Patient Department, Massachusetts General Hospital.

WEDNESDAY, JULY 28

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

SEPTEMBER 8–11. American Congress of Physical Therapy. Page 32, issue of July 1.

OCTOBER 11–22. 1943 Graduate Fortnight of the New York Academy of Medicine. Page 32, issue of July 1.

DISTRICT SOCIETIES

MIDDLESEX NORTH
JULY 28.

WORCESTER NORTH
JULY 28.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Text-Book of Pathology: An introduction to medicine. By William Boyd, M.D., LL.D., M.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.S.C., professor of pathology and bacteriology, University of Toronto. Fourth edition. 8°, cloth, 1008 pp., with 490 illustrations and 29 colored plates. Philadelphia: Lea and Febiger, 1943. $10.00.

This authoritative work has been thoroughly revised, and a considerable amount of material has been deleted. Among the principal deletions are the chapter "The Body Constants in Disease" and the sections on immunity and hypersensitiveness, which are dealt with more adequately in books on immunology. The section on principles of heredity, as well as much bacteriologic detail in the chapter "Bacterial Infections," has been omitted. Much new material has been added to the text to bring it up to date. A number of black-and-white illustrations and fourteen plates in color have been added, and many cuts and plates have been omitted.

Behind the Sulfa Drugs. By Iago Galdston, M.D. With a preface by Perrin H. Long, M.D., associate professor of medicine, Johns Hopkins University. 12°, cloth, 174 pp. New York City: D. Appleton-Century Company, Incorporated, 1943. $2.00.

This short history of a comparatively new field in treatment has been written for the layman. The first chapter deals with chemotherapy in ancient and modern times, with particular emphasis on the parts that Paracelsus and Robert Boyle played in this field. The first experimentally successful chemotherapeutic agent was a dye, and chapters are devoted to dyes and to Paul Ehrlich and salvarsan. In 1932, the new sulfanilamide compounds were first tested and since then the progress of this group has been remarkable and naturally can be treated only briefly in this small work, which is essentially a manual of the history of chemotherapy before the introduction of the sulfa compounds.

Collection "France Forever." Compiled by Professeur Henri Laugier. *Problèmes de Médecine de Guerre.* By Daniel Cordier. 12°, paper, 182 pp. *Les Relations Commerciales de la France.* By Jean Gottmann. 12°, paper, 211 pp. *Le Problème du Cancer.* By Charles Oberling. 12°, paper, 301 pp. Montreal: Les Éditions de l'Arbre, 1942.

France Forever is a Franco-American organization, representing the Free French movement in America. The above three titles are the first to appear in a series of small books, dealing with economic and scientific subjects. The medical problems of war, by Daniel Cordier, discusses insolation, artificial respiration, anesthesia and traumatic shock. The problem of cancer, by Oberling, is essentially a monograph on experimental cancer, preceded by an historical chapter on cancer and its theories. It is a rather comprehensive semipopular book.

A Handbook of Medical Library Practice. Based on a preliminary manuscript by M. Irene Jones. Compiled by a committee of the Medical Library Association. Edited by Janet Doe. 8°, cloth, 610 pp. Chicago: American Library Association, 1943. $5.00.

This handbook is the composite work of a number of librarians who are members of the Medical Library Association. It is designed as a manual for the newcomer, as well as for the experienced librarian. It has much material of value for those who are not in the medical-library profession, such as the chapter on rare books and the history of medicine, and there is a discussion on the growth and present status of medical libraries, in which the various types are discussed.

Terapeutica Al Dia. Anuario Terapéutico 1942: Compendio de las más notables contribuciones a la literatura médica aparecidas durante et ano. Compiled by Doctor Arturo R. Ros. 12°, cloth, 820 pp., illustrated: Habana, Cuba: Cultural S.A., 1943. $5.00.

This therapeutic manual is made up of abstracts in Spanish of articles published in the medical journals of all countries. The selection of notable articles for publication seems to be good. This work should be of considerable value for reference.